University of Michigan
Chemical Engineering Graduate Society

7th Annual 2018 Graduate Symposium

September 20th
Gerald R. Ford Library
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Awards

Outstanding Service Award

Excellence in Research Award

Excellence in Teaching Award

Oral Presentation Award

Poster Presentation Award
Graduate Symposium Committee

Head Chairs
Luke Bugada, Yixuan Chen, Sean Dix

Catering Chairs
Hannah Kim, Jiwoong Kang

Awards Chair
Kaylee Smith

Fundraising Chair
John Hemmerling
Schedule of Events

9:00 AM - 9:50 AM: Breakfast and Check-in
9:50 AM - 10:00 AM: Welcome
10:00 AM - 11:00 AM: Professor Darrell Irvine
          Keynote Address
11:00 AM - 12:30 PM: Student Oral Presentations, Session I
12:30 PM - 1:30 PM: Lunch
1:30 PM - 2:50 PM: Student Oral Presentations, Session II
2:50 PM - 3:00 PM: Coffee Break
3:00 PM - 3:50 PM: Student Oral Presentations, Session III
3:50 PM - 4:00 PM: Break
4:00 PM - 5:30 PM: Student Poster Presentations and Refreshments
5:30 PM - 6:30 PM: James Waldecker, PhD, Keynote Address
6:30 PM - 8:00 PM: Dinner, Awards, and Closing Remarks
## Oral Presentation Schedule

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Student Oral Presentations,  
Session I

Syntrophic co-culture amplification of production phenotype for high-throughput screening of microbial strain libraries

Tatyana Saleski¹, Alissa Kerner¹, Meng Ting Chung², Corine Jackman¹, Azzaya Khasbaatar¹, Katsuo Kurabayashi³, Xiaoxia Nina Lin¹
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²Department of Mechanical Engineering, University of Michigan, Ann Arbor, MI, USA

For most target molecules, the test phase of the design-build-test cycle remains a bottleneck for the development of microbial production strains by metabolic engineering. Here, we present a screening framework based on cross-feeding auxotrophs. Through a metabolic cross-feeding circuit, the production level of a target molecule is translated into co-culture growth characteristics, which amplifies differences in production performance into highly screenable growth phenotypes. This strategy can be applied to target molecules for which auxotrophic biosensors exist or can be created. We demonstrate this screening framework for two target molecules: 2-ketoisovalerate (a precursor of the drop-in biofuel isobutanol), and L-tryptophan. We show that the dynamic range of the screening may be tuned by employing an inhibitory analog of the target molecule. We also demonstrate that the strategy can be extended to screening for secondary metabolite production using a push-pull strategy. Screening based on this framework requires compartmentalization of individual producers with the sensor strain. We explore three formats of implementation with increasing throughput capability: confinement in microtiter plates, spatial separation on agar plates, and encapsulation in microdroplets. We employ the screening in the agar plate format to identify an efficient isobutanol production strain from a random mutagenesis library, reaching a final titer that is 5-fold higher than that of the parent strain. Finally, by fluorescence-activated droplet sorting, we show that super-producers in model libraries can be efficiently enriched from low frequencies at throughputs of >10⁶ library members/day.

Quantitative transport analysis of antibody-drug conjugates to predict cellular and tissue pharmacokinetics in solid tumors for designing effective clinical therapies

Eshita Khera¹, Cornelius Cilliers¹, Ian Nessler¹, Sumit Bhatnagar¹, Greg M. Thurber¹,².
¹Chemical Engineering, University of Michigan
²Biomedical Engineering, University of Michigan

Antibody-drug conjugates (ADC) have emerged as promising therapeutics for molecular targeting of cancer, with four recent FDA-approvals. Next-generation ADCs with impressive biophysical advances have recently seen a dramatic growth, but holistic evaluation of the impact of these innovations on clinical efficacy has not kept pace. Consequently, widespread clinical and commercial success continues to elude the field of ADC therapeutics. This lag may be attributed to the complex transport processes required for ADC delivery to the site of action. Specifically, the heterogeneous, perivascular tumoral distribution of ADCs is a well-known issue, and using joint experimental and computational work, we show how modifying the ADC physicochemical properties can help improve tumoral distribution. Experimentally, we demonstrate the influence of transport parameters like ADC extracellular diffusion and internalization rate in a 3-D tumor spheroid system. For example, JS91, a commonly studied anti-PSMA antibody shows heterogeneous distribution in PSMA-positive spheroids, accumulating in only 4-5 cell layers from the edge of the spheroid, which is similar to in vivo behavior, as confirmed by NIRF imaging in a mouse model and predictive simulations. “Bystander payloads” i.e. payloads that can diffuse out of targeted cells to kill nearby untargeted cells, can potentially also compensate for distribution heterogeneity. Since experimental techniques are not yet sensitive enough to directly measure payload distribution, we developed a predictive computational model that evaluates payload distribution as a function of controllable design parameters, aimed at determining bystander potential. Our simulations show that bystander effects can only partially compensate for poor ADC penetration, but are still critical for killing antigen negative tumor cells in clinical tumors. Payload bystander potential can be described by a dimensionless Damköhler number, Da (payload cellular uptake versus extracellular diffusion), and when Da is ~ 3, bystander payloads exhibit maximum tumor killing. Therefore, this combined experimental-simulation model system can quantitatively predict in vivo ADC distribution behavior in a controlled, systematic, and high-throughput manner, enabling the design of next-generation ADCs with improved clinical success.
Comparative study of Kupffer cells and liver sinusoidal endothelial cells in nanoparticle-induced antigen-specific immune tolerance

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2Department of Biomedical Engineering, University of Michigan
3School of Pharmacy, University of Maryland

Biodegradable nanoparticles (NPs) have demonstrated their potential to induce antigen (Ag)-specific immunological tolerance in autoimmune and allergy models. These peptide-containing poly(lactide-co-glycolide) (PLG) particles specifically suppress disease-associated T cells while preserving T cells necessary for protective immunity. Previous studies have implicated the spleen as the mediator of this tolerance; however, NPs induce tolerance in splenectomized animals. Additionally, most NPs administered intravenously accumulate in the liver. This study investigated the antigen presenting cells (APCs) of the liver, namely the Kupffer cells (KCs) and liver sinusoidal cells (LSECs), and their role in Ag-specific immune tolerance. Fluorescently labeled NPs associated with both cell types, but KCs scavenged more particles per cell. Phenotypical analysis of these cells showed that co-stimulatory molecules CD80 and CD86 (involved in immune activation) were unaffected, but co-inhibitory molecule PD-L1 (involved in tolerance) was upregulated. Investigation of T cell responses showed that both KCs and LSECs are capable of T cell activation and induced regulatory T cells, a phenotype that actively induces tolerance. The roles of KCs and LSECs in regulating immunity was studied in a mouse model of multiple sclerosis, experimental autoimmune encephalomyelitis (EAE). The role of the liver was isolated by splenectomizing individuals, and the contribution of LSECs was isolated by specifically depleting KCs with clodronate liposomes. KC depletion did not prevent immune tolerance by NP infusion indicating that KCs may not be required for NP-induced tolerance. Together, these results demonstrate the role of the liver in particle-induced tolerance and highlights the sufficiency of LSECs for this systemic tolerance.

Directed evolution of high affinity MDM2-binding ligands using stabilized bacterial peptide display

Tejas Navaratna, Lydia Atangcho, Andrew Min, Greg Thurber
Department of Chemical Engineering, University of Michigan

We developed SPEED (Stabilized Peptide Evolution by E. coli Display) to target interfaces between interacting proteins that include an alpha helix, the most common protein secondary structure motif. Such interfaces have posed attractive drug targets due to their importance in a wide range of diseases, in which inhibition, by blocking interactions, or activation, by triggering function, can result in therapeutic applications. However, due to the large size of protein-protein interaction surface areas, small molecules have seen little success in drug development. By incorporating azidohomoalanine (AHA) residues spaced 7 residues apart, we have demonstrated stabilization of peptides through double-click chemistry using a bifunctional linker. Such design allows for the inclusion of fluorophores for imaging applications or pharmacologic enhancers like PEG chains. Our lab and others have demonstrated that the resulting stabilized peptides have increased protease resistance, subcutaneous bioavailability, and binding affinities. Taking advantage of the ability of methionine auxotrophic E. coli to efficiently incorporate AHA as a methionine surrogate, we demonstrate efficient display of AHA incorporated peptide and robust reaction yields and specificity. As evidence of this method’s potential for diverse applications, we screened a stabilized peptide library with a diversity of 4 x 10^6 sequences based on the original p83 binding motif and obtained sequences with a greater than ~10-fold improvement in binding relative to the starting sequence (K_D = 1.8 nM) and discovered a novel and intriguing dual disulfide and chemical bridge structure.

Microdroplet co-cultivation and characterization of vaginal bacteria in vaginal fluid

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2Department of Biomedical Engineering, University of Michigan
3Department of Biological Sciences and the Initiative for Bioinformatics and Evolutionary Studies, University of Idaho
4Center for Computational Medicine and Bioinformatics, University of Michigan

The human vaginal microbiome (HVM) plays a fundamental role in women’s health and susceptibility to sexually transmitted infections (STIs). For instance, bacterial vaginosis (BV) is characterized by the depletion of lactobacilli and an overgrowth of fastidious and facultative anaerobes. BV is associated with infertility, preterm birth, and an increased risk of acquiring STIs like HIV. Cervicovaginal secretion (CVS) has been shown to decrease the rate of infectivity for HIV and demonstrate antimicrobial activity against nonresident bacteria. Despite the influence of CVS in the HVM, the ecological roles of many vaginal species and effects from the host still remain unclear. Current approaches for investigating them have severe limitations including a hampered ability to process small volumes of precious samples. In this work, we employed a microfluidic technology platform to encapsulate vaginal bacteria in CVS microdroplets. Our aim is to dissect bacterial inter-species interactions in the HVM while examining effects from CVS, which was also analyzed to screen for some small molecules that may contribute to inter-species interactions. Furthermore, the CVS that was used for cultivation was pooled from donors of reproductive age with similar microbial composition. Lactobacillus crispatus, a well-characterized vaginal species that is associated with promoting health in the vagina, was encapsulated in nano-liter microdroplets and underwent anaerobic incubation in CVS. Subsequently, analytical assays were carried out for characterization of these microdroplets. Our results show that microdroplet co-cultivation and characterization provide an effective means for identifying inter-species interactions in the HVM. Further extension of this approach and its future applications hold tremendous potential for novel ex vivo studies as shown in this work.
Hedgehog particles

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Particle stability is critical for development of new catalysts to produce sustainable fuels as well as sensors to detect bacteria and other pathogens. Hedgehog particles (HPs) replicating the spiky geometry of pollen grains reveal surprisingly high dispersion stability regardless of whether their polarity matches that of the solvent or not. This property designated as omnidispersibility is attributed to the drastic reduction of attractive van der Waals interactions between stiff nanoscale spikes of HPs compared to particles of the same dimensions with smooth surfaces. Here we show that HPs carrying dense conformal coatings made by layer-by-layer (LBL) assembly maintain dispersion stability in environments of extreme polarity and ionic strength. In addition, we expand HPs to new inert and active inorganic core materials including silica and hematite by utilizing LBL polyelectrolyte films. HPs surface-modified by multilayers of polymers and nanoparticles overcome the limited colloidal stability of other SERS probes resulting in greater than one order of magnitude increase of SERS intensity compared to colloids with smooth surfaces and simultaneous detection of several targets in complex media with high ionic strength. Inorganic HP dispersion stability enables catalysis in a nonpolar environment. Photocatalytic activity in a probe reaction in chloroform is achieved by the use of zinc oxide spikes as a template to form titanium dioxide spikes indicating promise for use in nonpolar processes such as cyclohexane oxidation. HPs enable fine-tuned control of intermolecular forces enabling stability in a wide array of chemical environments and applications in sensing, catalysis, and composites.
Student Oral Presentations, Session II

Use of nitrogen-containing carbon supports to control the acidity of supported heteropolyacid model catalysts

Xiaowen Zhao, Mark Barteau
Department of Chemical Engineering, University of Michigan, Ann Arbor

The physical and chemical properties of the heteropolyacids (HPAs) such as H3PMo12O40 (HPM) supported on nitrogen-containing carbon materials were investigated. Supports included two nitrogen-doped graphitic carbon samples, N-C-1000 (N atom% = 2%) and N-C-600 (N atom% = 19%), and mesoporous graphitic carbon nitride, mpgC3N4 (N atom% = 53%). The ability of these to disperse HPAs without crystallite formation followed the trend N-C-600 < N-C-1000 = activated carbon (C) < mpgC3N4. HPAs preferentially interact with pyridinic nitrogen and surface amino groups; the former lead to molecularly dispersed HPAs and the latter to ammonium HPA salt crystallites observed in XRD. At low coverage HPAs are molecularly dispersed on all four supports. Acid site populations at low coverages followed the trend: C = N-C-1000 > N-C-600 > mpgC3N4 as shown by 1-butene chemisorption. Using methanol oxidation as a probe reaction, the influence of these supports on catalyst dehydration and oxidation activity could be assessed. At comparable polyoxometalate (POM) anion coverages, C and N-C-1000 were similar with respect to their activities for these two reactions; however, supports with higher nitrogen concentration (N-C-600, mpgC3N4), gave rise to much lower activities for both reactions. The much greater decrease in dehydration activity vs. oxidation activity on these nitrogen-rich supports led to higher catalyst oxidation selectivity. This work demonstrates that acid site population of dispersed HPA catalysts can be controlled via nitrogen content of supports.

Programming self-organization of colloidal material at miniature scale

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2School of Engineering and Applied Sciences, Harvard University, Cambridge, Massachusetts 02138, USA
3Material Science and Engineering, University of Michigan, Ann Arbor, Michigan 48109, USA
4Biointerfaces Institute, University of Michigan, Ann Arbor, Michigan 48109, USA

Advancements in self-assembly and top-down fabrication approaches have enabled tailoring of colloidal material, macromolecules and nanoparticles in both organic and inorganic fashion to built advance functional materials. Through my research, using computer simulations and analytical modeling, I address building such material that are programmable at the elemental level and are tunable at the macroscopic level. In this talk I will discuss two approaches to this end that use active colloids (colloids possessing propulsion) as the raw material. This choice is motivated by the development in the field of active matter enabling synthesize using a wide variety of materials that can harness environmental energy into propulsion force. In the first approach, the system consists of particles that trigger propulsion only when in contact with other particles. Such system can be tuned externally to form and switch among crystals, gels and clusters. Further, these systems possess enhanced transport dynamics, which is also tunable. In the second approach, the active particles are connected end-to-end in a loop. When actuated, the loops fold into programmed shapes while the internal space is available to accommodate additional components such as sensors, controller, chemicals, and communication devices. The shape and motion information is encoded in the arrangement of active particles along the loop. Besides relevance of these systems in understanding the fundamental physics of non-equilibrium systems, they can be used to develop smart materials that can sense, actuate, compute and communicate.

Elucidating mechanisms of plasmon decay in multimetallic nanostructures for the rational design of plasmonic photocatalysts

Steven Chavez, Umar Aslam, SuJio Linic
Department of Chemical Engineering, University of Michigan – Ann Arbor

Plasmonic metal nanoparticles are promising platforms for manipulating the flow of electromagnetic energy at the nanometer length scale. Upon light illumination, plasmonic nanoparticles act to confine the energy of incoming radiation in the form of amplified electromagnetic fields at their surface. The energy of these fields can then be dissipated either through radiative scattering of photons or non-radiative excitation of energetic charge carriers (i.e. absorption) in the metal nanoparticle. Recently, there has been increasing interest in controlling these plasmon decay processes with the ultimate goal of designing nanostructures with highly localized charge carrier generation at specific locations in the nanoparticle. For example, manipulating the location of the charge carrier excitation (photon absorption) in terms of surface versus bulk excitations is critical in a number of applications, including plasmonic photocatalysis. In this contribution, we shed light on the physical framework describing the flow of energy in multimetallic plasmonic
nanoparticles. We do so by systematically investigating, through experimental and modeling approaches, the LSPR decay mechanisms in Ag-Pt and Au-Pt core-shell nanoparticles of different shapes and sizes. We demonstrate that coating plasmonic nanostructures with non-plasmonic metals can result in the preferential dissipation of energy through the surface layers of the nanoparticles. We show that the extent of this energy dissipation depends heavily on the electronic structure of the constituent metals. We conclude by providing insights into how this physical framework can aid the rational design of multicomponent plasmonic for plasmonic photocatalysis.

Shear banding and its impact on bulk rheology in a thixotropic yield-stress fluid

Yufei Wei, Michael J. Solomon, Ronald G. Larson
Department of Chemical Engineering, University of Michigan, Ann Arbor

Many complex fluids, such as paints, waxy crude oils, and human blood, are thixotropic yield-stress fluids – they flow only if the external force exceeds a certain limit and under flow, their viscosity, moduli, and yield stress gradually decrease. Those rheological properties, however, slowly build up when flow stops. Shear banding often occurs in thixotropic yield-stress fluids in which the initially homogeneous shear flow separates into bands with different local shear rates. We use time-resolved particle image velocimetry with a high spatial resolution to study the onset and evolution of shear bands in a fumed silica suspension, a thixotropic yield-stress fluid. This fluid exhibits rich spatiotemporal dynamics of local velocimetry, including shear bands that evolve slowly, quickly homogenize, and periodically oscillate, none of which has been in previous studies. We construct a simple constitutive model to explain the oscillatory banding dynamics and show that the velocimetry oscillation is caused by the instability of the nonlinear rheology.

A self-organization route to three-dimensional chiral metamaterials

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2Department of Materials Science and Engineering, University of Michigan, Ann Arbor

Controlled formation of three-dimensional (3D) chiral structures offers a pathway to the realization of new and unusual light-matter interactions, such as negative refraction, perfect absorption, and enhanced nonlinear optical properties. Top-down lithographic methods have successfully been used to fabricate complex 3D chiral architectures with micrometer-scale characteristic dimensions, but their wider application toward large-area materials remains challenging. Here, we report a bottom-up route based on directional solidification of eutectic spirals. During solidification of a eutectic melt, the liquid phase-separates simultaneously into two (or more) solid phases which self-organize into alternating monoliths. We demonstrate a class of faceted eutectic spirals in the Zn-Mg alloy system. By independently tuning the thermal gradient (G) as well as velocity (V) of the solidification front, we steer the system down different kinetic pathways to produce various eutectic morphologies, trapping the system as metastable, two-phase conical eutectic spirals with opposite chirality at moderate G and high V. To better understand the emergence of such structures from a parent liquid phase, we have conducted a multimodal investigation using X-ray nanotomography, 3D electron backscatter diffraction, and further electron microscopy. Our correlative imaging workflow provides new insights into the complex morphology, crystallography, and underlying growth mechanism of the faceted eutectic spirals. It is anticipated that these results will provide the necessary benchmark data for simulations (e.g., phase field) of multiphase solidification patterns.
Student Oral Presentations,
Session III

Two-color photo-inhibition for continuous additive manufacturing

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$^2$Department of Macromolecular Science & Engineering, University of Michigan
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Additive manufacturing (AM), also known as 3D-printing, is exciting disruptive technology that may upend contemporary manufacturing practices. Production in AM generally proceeds by layer-by-layer addition of material—typically thermoplastic or photopolymerizable resin—to gradually build up the desired geometry, allowing for the production of highly individualized parts with near limitless complexity. The achievable print speed is still one of the major limitations of the current technologies with layer-by-layer devices only able to achieve vertical print speeds of several millimeters per hour. Recently, a layer-less (or continuous) method for resin based AM, termed continuous liquid interface production, was developed. The method relies on a thin diffusion-controlled oxygen-inhibited dead zone to eliminate adhesion to the projection window during printing, allowing for an order of magnitude increase in the achievable printing speeds when compared with traditional SLA devices. Photo-inhibitor molecules that inhibit polymerization in the presence of light may be an attractive alternative inhibition mechanism to oxygen-inhibited systems. The advantages of this type of system are that diffusion of oxygen no longer controls the thickness of the dead zone, and the limit of this zone is theoretically much larger. Larger dead zones allow faster polymer reflow under the printing part and, therefore, faster build speeds. This talk will present a novel method using a two-color irradiation scheme to spatially control polymerization to generate dead zones for rapid AM and enable additional functionality over conventional continuous additive manufacturing methods.

Flow instability in aqueous chitosan solutions: concentration dependent rheology and velocimetry

Nina Gasbarro$^1$ and Michael J. Solomon$^1$
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Chitosan and its derivatives are of interest due to their versatility and potential both as a biomaterial and additive for rheological control. We report that aqueous solutions of chitosan with concentration 3 mg/ml (c/c* = 1.8, where c* is the overlap concentration) and greater display a regime of shear thinning at low shear rates that is consistent with the existence of a yield or plateau stress. We probe the physicochemical, microdynamical, and kinematic origins of this rheological behavior by the addition of urea – a hydrogen bond and hydrophobic interaction disrupter, by dynamic light scattering (DLS), and by direct measurement of the velocity profile in rotational shear flow. We find that the effect of urea on the qualitative features of this rheological behavior is limited. DLS of chitosan at high concentrations indicates extremely slow microdynamics, consistent with the presence of a network or glassy fluid of large, associated aggregates. Direct measurement of the velocity profile in these flows using particle tracking velocimetry identifies a correlation between the plateau stress and the observation of shear banded flow.

Making sense of noisy dynamic cell signaling data

Phillip Spinoso, Jennifer Linderman
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Single-cell data is becoming increasingly available as bulk measurements of cell populations prove insufficient to characterize cell signaling behavior. Two advantages of single-cell data are the ability to investigate heterogeneity and capture a large amount of data in a single experiment. However, methods of extracting information from such heterogeneous, noisy data are lacking. Here we combine time-lapse imaging with computational modeling of two common signaling pathways, Akt and ERK, to examine dynamic heterogeneous cell signaling responses to an input stimulus. By exploiting the sheer quantity of single-cell dynamic data, we developed a noise reduction method which assumes random noise occurs independently of signal when comparing single cells. Although our single-cell signaling data is heterogeneous, the heterogeneity is reproducible, suggesting that there is an inherent order to the system. Therefore, we outline how an ordinary differential equation model featuring extrinsic noise can provide a structure to understand how heterogeneity adjusts the balance of opposing forces in complex cell signaling data. Because of the heterogeneity in basal state as well as signaling potential, we propose specific upstream and downstream regulators of signaling must be variable (extrinsic noise) by means outside of the specific ligand-receptor interaction. By using the computational model to probe the design space of single-cell responses to a ligand-receptor stimulus, we can deduce the extrinsic noise parameters present in individual cells and uncover the intracellular settings which drive them to behave so heterogeneously. Our model predicts signaling behaviors from three breast cancer cell lines, validating its robustness and generalizability. Our findings demonstrate how seemingly heterogeneous single-cell data can contain useful insight into cell signaling pathways, and how computational models can undermine the complexity of signaling networks.
Student Poster Presentations

Rigid red blood cell impact on platelet adhesion in an acute vascular injury model

Alison L. Banka¹, Mario Gutierrez¹, Tyler Tanski¹, and Omolola Eniola-Adefeso¹
¹Department of Chemical Engineering, University of Michigan

Platelets are a key component of blood whose primary function is to maintain hemostasis by rapidly plugging any interruptions in the vasculature, a process known as clotting. Clotting is key to the physiological response to vascular injury, preventing excessive blood loss, permanent damage, and even death. Clotting is initiated after damage to the endothelium, causing platelets to active and bind to the endothelium or exposed extracellular matrix proteins. Platelet margination and binding to the vascular wall is promoted through hemodynamic, heterogenous collisions between cells, including deformable red blood cells (RBCs) in the RBC core. A hallmark of sickle cell disease (SCD) is the membrane rigidification and sickling of RBCs, which combined with other inflamed cell types lead to vaso-occlusive crises (VOC) in many patients. Despite the increase in VOC for SCD patients, little experimental work exists to fully elucidate the effect of rigid RBCs on platelet margination and binding in vessels. We utilized an in vitro flow-based system to examine how the extent of rigidification and rigid RBC concentration affect platelet margination and binding to a damaged endothelium model mimicking acute vascular damage. We determined that the inclusion of rigid RBCs increases platelet adhesion to a damaged endothelium in flow and that the extent of adhesion is dependent on several key variables, including the RBC fraction rigidified and extent of rigidification. Overall, this study can help elucidate how rigid RBC/platelet interactions can contribute to VOC in SCD patients.

Heat as a novel treatment of Staphylococcus epidermidis biofilms in an in vitro flow cell model

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²Department of Emergency Medicine, University of Michigan, Ann Arbor, MI

Contamination of implanted medical devices by bacterial biofilms causes significant morbidity and mortality. Currently, the standard of care is to surgically remove infected devices and replace them, which is costly and further increases morbidity and mortality. Understanding biofilm development as the consequence of adsorption, growth and detachment with each effect governed by self-assembly, fluid mechanics and transport phenomena, we translate the use of heat as a potential anti-biofilm therapy in a physiologically relevant flow model. We developed an in vitro biofilm reactor system to mimic the physiologic conditions surrounding a dialysis catheter. Staphylococcus epidermidis was seeded and grown at 37°C to establish a mature biofilm. Then the temperature of the infusate was held at 37°C or increased to 45°C, 50°C, or 60°C. Cell viability was determined by confocal microscopy using Live/Dead staining and quantitative culture techniques. Biofilms morphology was characterized from confocal microscopy images using Fast Fourier Transform analysis. The percentage of live cells decreased from 89% ± 2% at 37°C, to 87% ± 2% at 45°C, 64% ± 6% at 50°C and 27% ± 3% at 60°C treatments. There was a tenfold reduction in the number of colony forming units from 37°C to 45°C and a greater than three log reduction for both 50°C and 60°C treatments. We also observed a dramatic increase in the structural heterogeneity with elevated temperature treatment on macro-, meso-, and microscopic scales. Exposing biofilms to elevated temperatures changes both the morphology and cell viability of the biofilm. Understanding the response of these bacterial cells under thermal stress is a promising step toward the development of an in vitro treatment/remediation method for biofilm growth in medical devices.

Ultrathin plasmonic coatings for selective radiative transmission in silica aerogels

¹Department of Chemical Engineering, University of Michigan

Current solar thermal collectors use vacuum insulation which only partially blocks outgoing infrared radiation from the absorbing surface. The losses associated with this phenomenon lead to a decrease in collector performance due to a reduction in temperature or efficiency. Visibly-transparent silica aerogels are a promising alternative to vacuum insulation in solar thermal applications. However, they are also characterized by undesirable transmission in the mid-infrared band. Here, we investigate ultrathin conformal plasmonic coatings to selectively enhance the absorption of silica aerogels in this target band and suppress outgoing radiative losses at high temperatures. We fabricated aerogels coated with aluminum-doped zinc oxide (AZO) using atomic-layer deposition (ALD). An evaluation of the microstructure via electron microscopy confirms that ALD is a suitable technique for the conformal coating of aerogels. Furthermore, we characterize the effect of the AZO coatings on the optical and thermal properties. We demonstrate AZO-coated aerogels with high solar transmission and low infrared transmission. The absorption coefficient in the target mid-infrared band increases substantially due to the AZO. In contrast, transmission of solar radiation through the materials was not significantly impacted. Ultrathin plasmonic coatings have the potential to significantly improve the performance of low-irradiance, high-temperature solar collectors.
Thin films for enhanced photon recycle in thermophotovoltaics

Tobias Burger¹, Deju Fan², Kyusang Lee³, Stephen R. Forrest², Andrej Lenert¹
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²Department of Electrical and Computer Engineering, University of Michigan, Ann Arbor, MI 48109
³Department of Electrical and Computer Engineering, and Materials Science and Engineering, University of Virginia, Charlottesville, VA 22903

Thermophotovoltaics (TPVs) are a promising, solid-state technology for distributed electricity generation. To achieve high conversion efficiency in TPV systems, it is necessary to suppress transport between the thermal emitter and PV cell. Targeted design of thermal emitters exhibiting selective emission of above-bandgap radiation has enabled improved efficiency over systems characterized by broadband radiative transfer. However, the selectivity of these emitters degrades at the high source temperatures required by TPV conversion. Selectively absorptive cells achieve sub-bandgap suppression by low-energy photon recycle, enabling spectral selectivity in systems with broadband emitters. However, conventional, substrate-containing devices exhibit limited sub-bandgap reflectance, inhibiting the effectiveness of photon recycle for absorptive spectral control. Here, we demonstrate thin-film, intrinsic InGaAsAs structures with improved spectral selectivity and develop an optimization tool for facilitating design of selectively absorptive thin-film TPV generators.

How do bacterial and host variability influence treatment of tuberculosis?

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Tuberculosis (TB) is one of the world’s deadliest infectious diseases. Caused by infection with Mycobacterium tuberculosis (Mtbt), treatment of drug-susceptible TB often requires greater than six months of therapy with multiple antibiotics. The main pathological feature of TB is the formation of a granuloma in infected lung tissue, which serves as an immunological response to contain the infection, but also can present a physiological barrier to antibiotic diffusion and a home for antibiotic-tolerant bacteria. Using a multi-scale, computational model of granuloma formation and antibiotic pharmacokinetics (PK) and pharmacodynamics (PD), we can simulate how antibiotic therapy assists in granuloma sterilization. However, capturing the observed range of responses to therapies requires incorporating appropriate biological variability into these models. Here we discuss a method for modeling the PK of first line TB antibiotics that captures the variability in plasma PK among patients, as well as the variability in tissue PK that exists between granulomas within a patient. Using dose-response data to measure bactericidal activity of antibiotics on Mtbt under various conditions, we predict the concentration dependent killing activity on the different phenotypes of Mtbt in the computational model. By capturing the appropriate variability in these treatment simulations, we can generate a more complete prediction of how antibiotic therapy can sterilize, or fail to sterilize, granulomas.

Designing antibody libraries with drug-like antibody specificity

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Antibody specificity is arguably the most important and challenging property to optimize during in vitro antibody selection and affinity maturation. We have sought to develop methods for both designing and sorting antibody libraries that maximize the specificity of the selected variants. First, we have developed a novel library design method that samples wild-type residues and a small number of the most frequently occurring residues at each position of antibody binding loops based on natural antibody diversity. Second, we have developed methods for performing strong negative selections using different types of polyspecificity reagents (e.g., non-target proteins and peptides) and strong positive selections against the targets of interest. Importantly, we find that our library design and selection methods result in antibody variants with unusually high specificity. Further, these variants are enriched in polar/aromatic residues (tyrosine) and negatively charged residues (aspartic acid) in the binding loops, and this appears linked to their drug-like specificity. We are currently using these insights to generate novel antibody libraries that sample tyrosine, aspartic acid and other residues in their binding loops that are favorable for high antibody specificity in several (~50) different antibody frameworks. We will discuss how we are using these and related approaches to improve in vitro isolation of antibodies with drug-like properties.

Parallel competing reaction pathways for CO₂ reduction by Rh nanocluster and single-atom catalysts on TiO₂

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Many heterogeneous catalysts consist of supported metal nanoclusters, which allow for more exposed metal surface area and a greater number of under-coordinated atomic sites compared to bulk metal. Metal cluster morphology can change dynamically under reaction conditions, and even cluster disintegration into single metal ions can occur. In some cases, these isolated metal ions are responsible for enhanced catalytic activity or selectivity compared to metal nanoclusters and nanoparticles. We aim here to understand the reduction of CO₂ via H₂ using a Rh/TiO₂ catalyst. It is known that Rh single atoms (Rh₁) promote the reverse water-
gas shift reaction (RWGSR) to form CO and water, whereas Rh nanoclusters drive a parallel competing reaction pathway to produce CH₄. However, the critical Rh nanocluster size where catalytic methanation is promoted over the RWGSR remains unknown. We hypothesize that a cluster of at least four Rh atoms is required to catalyze the methanation reaction, based on the need for additional binding sites of H₂ and the higher number of electrons transferred compared to RWGSR. Kohn-sham DFT calculations using the PBE exchange correlation functional are performed to examine the RWGSR and catalytic methanation on Rh₇/TiO₂ (x = 1–8) to understand the impact of nanocluster size and morphology on activity and selectivity. Using a genetic algorithm and grand canonical Monte Carlo methods, we determine the most stable configurations of Rh₇-Rh₈ nanoclusters on TiO₂ with and without reactants covering the surface. After, we calculate important transition states along the RWGSR and methanation reaction pathways at each nanocluster size to discover the important crossover point where one reaction becomes preferred over the other.

Active metal redispersion in palladium core@shell nanoparticles: Enhancing thermal stability and activity in three-way automotive catalysts

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Increasingly stringent fuel efficiency standards for gasoline combustion engines are resulting in lower exhaust temperatures. Consequently, enhanced three-way catalysts that can achieve light off at significantly lower temperatures than current systems (~250–300 °C) are needed. Concurrently, any new catalyst must maintain thermal stability and activity even after prolonged aging at temperatures exceeding 850 °C. Both goals may be addressed by a core@shell architecture where a nanoscale metal particle is encapsulated by a porous metal oxide shell such as silica or ceria. The reducibility exhibited by oxides such as ceria allows for the reversible storage and release of oxygen. This facilitates a low energy reaction mechanism at the interface between the metal particle and oxide. Core@shell morphology — through encapsulation — maximizes expression of these highly active sites, resulting in appreciable enhancement in catalytic activity. Counterintuitively, these catalysts exhibit improved performance after severe aging, in contrast to the behavior of commercial catalysts. This improved performance is related to the re-dispersion of metal atoms throughout the porous shell structure, which is facilitated by a temperature and atmosphere dependent metal/metal oxide transition. This work examines the temporal nature of this re-dispersion and strives to decouple the atmospheric and atomic oxygen contributions responsible for metal/metal oxide transitions through synthesized Pd@SiO2 and Pd@CeO2 catalysts. The insights gained from this research remark on the applicability of core@shell nanoparticles as robust three-way catalyst elements with low-temperature light off, high stability and activity.

Reconfigurable light diffraction response of ellipsoidal colloids by electric field assisted assembly

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Colloids self-assemble to a variety of crystalline forms with the potential for vibrant structural color. However, the fundamental relationship between the quality of the real space crystal structure (microscopic-scale defect arrangement) and the intensity of the light diffraction response (macroscopic-scale) remains poorly understood. In this study, we use alternating current (AC) electric field assisted assembly to produce millimeter-scale arrays of ellipsoidal colloids. Compared to spheres, these particles possess an additional rotational degree of freedom for tailoring the optical/structural properties of the assembly. Small-angle light scattering (SALS) is used to quantify the light diffraction response. The time-resolved SALS probes the kinetics of positional and orientational ordering in the self-assembled anisotropic structures, which have complex symmetry. The ordered colloidal structures are created with polystyrene ellipsoids of aspect ratio 2.04 (major axis 6.54 μm and minor axis 3.2 μm). Here, we show three different light diffraction patterns measured from different real space structures: a phase with neither orientational nor positional order (fluid), a phase with high orientational order (chain-like structure), and a phase with high positional and orientational order (close-packed structure). Differences in light diffraction patterns peak area demonstrate differences in long-range ordering. We then demonstrate methods to improve the quality of the colloidal crystals through optimization of the applied electric-field strength and frequency. We finally present a combined experimental and computational approach to investigate the shape effect on colloids ordering kinetics. This research contributes to the understanding of optical properties of anisotropic colloidal crystals, and is useful for designing the brilliance of structural color at visible and infrared wavelengths.

Heteroatom and side-chain effects on the optical properties: ultrafast and nonlinear spectroscopy of new naptho[1,2-b:5,6-b']difuran donor organic photovoltaic (OPV) polymers

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Conjugated polymers are promising alternatives to inorganic semiconductors in a wide range of electronic applications such as organic photovoltaics (OPVs), organic thin film transistors, and sensors. Understanding the optical properties of these materials shed light to the electron-photon interactions (i.e. structure-function relationships) that occur in the molecular level within these materials. Photophysical properties of four novel conjugated donor OPV polymers with naptho[1,2-b:5,6-b]difuran as the donor moiety and either 3,6-di(furan-2-yl)-1,4-diketopyrrolo[3,4-c]pyrrole or 3,6-di(thiophen-2-yl)-1,4-diketopyrrolo[3,4-c]pyrrole were investigated to understand the influence of heteroatoms in the polymer backbone. The sidechains were varied as well to study the effect of polymer solubility on these properties. Steady state absorption studies showed that the polymer with furan backbone displayed a favorable tendency of capturing more solar photons when used in a photovoltaic device. Fluorescence lifetime was monitored using ultrafast dynamics, and the results obtained show that the kind of heteroatom used in the backbone affects the decay dynamics of the polymer; the side chain also plays a subtle role in determining the fluorescence decay time. Theoretical calculations confirm the two-photon absorption cross-section (TPA-5) results obtained, illustrating the planarity of the molecules in relation to its torsional angles. The natural transition orbitals were also computed, describing the electron and hole transition orbitals for each of the molecule. A pump-probe technique was employed to probe the non-emissive and charge transfer states of the polymers.

Hybrid agent-based model to predict drug delivery to heterogeneous tumors overexpressing HER2

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Trastuzumab emtansine (T-DM1), an antibody-drug conjugate (ADC) approved by the FDA, has demonstrated the ability to extend survival in tumors with HER2 overexpression. The efficacy of this treatment is affected by ADC pharmacokinetics and pharmacodynamics in the tumor environment. For example, some tumor vessels are leaky, have poor blood flow, and/or are not able to deliver oxygen, nutrients, and drugs through transient or chronic lack of perfusion (i.e. non-functional vessels). New vessels also appear through the process of angiogenesis. Tumor histology shows that most T-DM1 localizes around blood vessels, but co-administration with its unconjugated form (trastuzumab) improves penetration of the ADC into the tumor and subsequent treatment efficacy. ADC dosing schedule has also been shown to contribute to drug efficacy and tolerability. However, it is still not clear how deeper tissue penetration combined with different dosing regimens might improve efficacy. Here, we develop a hybrid agent-based model (ABM) to capture drug delivery and to predict tumor killing and growth kinetics that enables detailed depictions of heterogeneous delivery, cancer cell death, vascularization, tumor growth, and drug regimens. Simulation of drug treatment regimens, presented here as combinations of T-DM1 and its unconjugated form, provide an inexpensive method for examining factors relevant to drug efficacy that are impractical using large tumor samples. Compared to previously used continuous models, the ABM framework model is able to simulate drug distribution in the scenario of multiple blood vessels and cancer cells that behave independently of one another and is a platform to guide the development of more effective ADC treatment.

Single-cell tumor metabolism of immune checkpoint inhibitors determines optimal dosing for this class of antibody therapeutics

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Next-generation therapeutics, such as immune checkpoint inhibitors, frequently lack a relevant maximum tolerated dose, making clinical dose estimation challenging. In the absence of an upper bound due to toxicity, the focus is placed on efficacy. Similar to many non-chemotherapy drugs, the maximum efficacy occurs when the target is saturated. However, the relationship between systemic plasma concentration and receptor occupancy at the site of action within a tumor is complex. This is particularly acute with the dynamic expression of immune checkpoint proteins such as PD-1 and PD-L1 that have widely varying expression levels on multiple cell types that can change dramatically during treatment. In this work, we used near-infrared fluorescence ratio imaging to quantify tumor antibody uptake and metabolism. Specifically, anti-PD-1 and anti-PD-L1 antibodies were dually labelled with a residualizing near-infrared (NIR) fluorescent dye (that is trapped within the cell following metabolism) and a non-residualizing NIR dye that washes away. By harvesting the treated tumors, generating a single-cell digest, and analysing the relative ratio of the NIR dyes by flow cytometry, we were able to measure single-cell binding and metabolism of the antibodies on different cell populations within the tumor (e.g. tumor cells, T-cells, and macrophages). The results highlight tumor metabolism as one of the defining parameters for clinical dosing of these drugs. Strikingly, this is not a routine measurement during drug development. Likewise, the results show that systemic clearance and plasma markers can be misleading when determining target saturation within the tumor microenvironment.

Analysis of non-small cell lung cancer circulating tumor cells using a graphene oxide based microfluidic device

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Approximately 14% of all new cancers are lung cancers, and of those lung cancers, 80% are non-small cell lung cancer (NSCLC). Advancements in metastatic NSCLC treatment have led to the use of antibodies against programmed death ligand 1 (PD-L1) as a checkpoint inhibitor to stop the deactivation of T-cells associated with PD-1-PD-L1 interactions. Currently, all patients undergo
chemoradiation treatment followed immediately by durvalumab, an anti-PD-L1 antibody. It is not, however, understood which patients will benefit from this incredibly expensive treatment. Current methods for PD-L1 assessment require performing immunohistochemistry of a lung tissue biopsy, a particularly invasive procedure. We use circulating tumor cells (CTCs), a rare cell found in a patient's peripheral blood, to monitor disease progression and determine the PD-L1 status of the patient. We aim to predict which patients will benefit from the immunotherapy durvalumab. In this study, we look at the changes in CTC counts, PD-L1 expression of a patient's CTCs, mRNA, and miRNA expression over the course of their chemoradiation therapy. We use a graphene oxide based microfluidic chip (GO Chip) to isolate CTCs using antibodies against cellular markers found in NSCLC. Our capture antibodies are EPCAM, CD133 and EGFR. We then stain the cells for cytokeratin, CD45, DAPI and, PD-L1, with cytokeratin and DAPI positive cells being CTCs. Additionally, we are interrogating the CTCs for 96-genes of interest, including PD-L1, to increase our understanding of the CTC landscape in NSCLC. Finally, we are working in collaboration with clinicians to investigate the changes in miRNA profiles over the course of chemoradiation treatments.

Developing an in vivo predictive dissolution device to simulate the human gastrointestinal (GI) tract and advance oral drug product optimization and bioequivalence (BE) evaluation.

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Solid oral dosage forms are being absorbed into the intestinal mucosal cells after being dissolved in the small intestine. Thus, drug dissolution is a key process in oral drug delivery which is controlled by physiological elements such as buffer capacity, pH, gastric emptying rate, intestinal motility, and hydrodynamics. These physiological factors influence the drug dissolution as well as drug absorption and drug plasma level. The current compendial dissolution tests do not mimic the physiological environment. Therefore, learning in vivo conditions which are rate-determining for dissolution and utilizing them into an in vitro dissolution test, can fulfill the quality control purposes as well as accomplishing a sensible in vitro / in vivo correlation (IVIVC). Amongst the physiological parameters determining the drug dissolution rate the effect of buffer species, pH, buffer capacity as well as the hydrodynamics are predominant. There is a need to develop a biorelevant, predictive dissolution method that can be applied by pharmaceutical companies to facilitate marketing access for generic and novel drug products. In a recent clinical and computational study performed between the University of Michigan, University of Nottingham, and Pennsylvania State University, University of Colorado, the critical factors deriving the dissolution and absorption in the human GI tract have been more accurately determined. The primary goal of the proposed research is understanding the rate determining factors for ionizable drug dissolutions from in vitro studies, real time magnetic resonance imaging (MRI) manometry, and computational fluid dynamic simulations (CFD) done by this recent study and taking advantage of a mechanistic mass transport model to quantify the GI tract hydrodynamical and environmental parameters and incorporating the in vivo knowledge to a practical, useful, reliable and effective in vitro dissolution apparatus that can simulate the in vivo drug dissolution rate in the GI tract. A mechanistic mass transport model for the immediately disintegrating weak acid dosage forms dissolution in in vitro condition that can ultimately be used to simulate the in vivo drug dissolution rate in human is suggested. Moreover, a mass transport model for acidic and basic drug dissolution in bicarbonate medium was developed considering the effect of hydration and dehydration reaction rates of bicarbonate buffer. An agreement between the simulated and experimental dissolution rates lends credibility to use this model for a range of drugs, with various particle size distributions dissolving under distinct physiological conditions in the gastrointestinal (GI) tract. Moreover, a CFD-based method was applied to quantify the hydrodynamical parameters of the current gastrointestinal system simulator (GIS I). The calculated hydrodynamical parameters were validated by the dissolution experiments. The validated CFD method was utilized to design a physiological-relevant in vitro system for GI tract (GIS II) focusing on the in vivo hydrodynamical conditions and optimizing the particle suspension to generate reproducible dissolution test results. The new design of dissolution bowl and stirers as well as the operating conditions are the outcomes of an attempt to simulate the in vivo hydrodynamical conditions for oral dosage forms.

Monitoring hepatocellular carcinoma from circulating tumor cells

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Hepatocellular carcinoma is the most common primary liver malignancy and has a two year recurrence free rate of 9.1%. Recurrence is believed to be initiated through metastasis, or the spread of the initial cancer to other areas of the body; metastasis is likely caused by circulating tumor cells (CTCs), which are rare cancer cells found in the blood stream. CTCs are believed to be released from all solid cancers and can be used for liquid biopsies in the place of tissue biopsies. Analysis of CTCs could allow for less invasive diagnostics and the ability to actively monitor changes in the cancer throughout treatment. Because CTCs are extremely rare with on the order of 1 CTC present per million mononuclear cells, high sensitivity tests are necessary to isolate CTCs. In this study, the Labyrinth, an inertial microfluidic sorting device, was used to isolate CTCs from blood. The red blood cells are first removed from the blood and then the blood is diluted. The Labyrinth separates the remaining cells in this sample by size, based on the differing forces the cells experience. Since cancer cells tend to be larger than white blood cells, they can be separated effectively. This study analyzed 10 mL blood samples from 40 patients. The samples were stained with the antibody cocktail hepx par 1, glypican 3, and glutamine synthetase to identify them as CTCs or white blood cells. They were also stained for a known epithelial to mesenchymal transition marker, which has been associated with increased metastasis. These results can then be compared to patient information to determine our ability to monitor hepatocellular carcinoma.
Polymer scaffolds for early detection and vaccination against metastatic breast cancer

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The formation of distant metastasis is the point at which cancer is often no longer curable and eventually leads to mortality. Development of methods for early detection and early treatment of metastasis could dramatically improve survival. The Shea and Jeruss laboratories have developed biomaterial scaffolds that recruit metastatic tumor cells in several mouse models of cancer. Scaffolds also provide a platform to deliver immunostimulatory factors or cells to elicit immunity against cancer cells in a controlled microenvironment. The addition of allogeneic stimulation to the scaffolds can enhance anti-tumor response by increasing the repertoire of T cells ready to respond to challenge with tumor antigens. Here we investigate the potential of PCL scaffolds for both early detection and allogeneic tumor vaccine delivery in the E0771 syngeneic mouse model of metastatic breast cancer in C57BL/6 mice. PCL scaffolds were found to recruit GFP\textsuperscript{+} metastatic tumor cells in both the E0771 and E0771-Br2 mouse model of breast cancer, prior to physical indications of metastatic disease, suggesting that these scaffolds can be used for early detection of metastasis and to monitor disease progression. The scaffold-based cancer vaccine prevented primary tumor engraftment, delayed disease progression, and resulted in long-term disease-free survival. Finally, the addition of allogeneic stimulation resulted in antitumor immunity, and enhanced disease-free survival, suggesting allogeneic stimulation may serve as a potent adjuvant.

Physicochemical rules for identifying monoclonal antibodies with drug-like specificity

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The ability of antibodies to recognize their target antigens with high specificity is fundamental to their normal function. Nevertheless, therapeutic antibodies display variable and difficult-to-predict levels of non-specific (heterotypic) and self- (homotypic) interactions that lead to various drug development challenges, including antibody aggregation, abnormally high viscosity and fast antibody clearance. We are developing the first bioinformatics method for predicting the overall specificity of antibodies in terms of their relative risk for displaying high levels of non-specific and self-interactions. We find that individual and combined sets of chemical rules that limit the maximum allowable sum of positively charged and hydrophobic residues and minimum allowable sum of polar and negatively charged residues in different parts of the variable regions of antibodies are excellent predictors of specificity for diverse panels of antibodies, including >100 clinical-stage antibodies. These finding can be readily used to improve antibody selection and engineering to generate antibodies with drug-like specificity.

Inverse crystal design for target materials properties

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Inverse design is a promising yet still challenging approach to the development of new materials with desired properties. To date, several methods exist for the design of pairwise interaction potentials that stabilize target crystal structures. If one knows how property is related to structure, then inverse design of a structure is essentially inverse design of a property. In the absence of such knowledge, however, new approaches are needed. We present results of molecular dynamics simulations of crystals self-assembled via a family of pair potentials, with a materials property bias added to the system Hamiltonian as an energy penalty. In this manner, we determine the thermodynamically optimal form of the pair potential that leads to self-assembled structures with targeted materials properties.