PHYSICOCHEMICAL FUNDAMENTALS OF DNA HYBRIDIZATIONS ON SURFACES

AS APPLIED TO MICROARRAYS AND BEAD-BASED SEQUENCING TECHNOLOGIES

INTERNATIONAL WORKSHOP

Ploen, Germany, May 9 – 12, 2011

Organizers:

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Ploen

Ploen is a small beautiful town in the Land of Schleswig-Holstein, northern Germany. It is the home of the Max Planck Institute for Evolutionary Biology, which is hosting the workshop. In Ploen, there is a gorgeous castle, and there are thousands of lakes around making the area a wonderful tourist attraction in spring and summer!

Conference Abstract

Many fields of biological science depend upon accurate identification and quantification of nucleic acid targets because these targets indirectly reflect the state of a biological system. Oligonucleotide microarrays were once thought to be the big hope for the high-throughput identification and quantification of nucleic acids. At that time, it was believed that designing probes for microarrays and interpreting results was mostly a bioinformatics/statistical exercise. However, it turned out, that interpreting the signal from microarrays was a major challenge in terms of surface chemistry because many details, such as the interactions between nucleic acid targets in solution and oligonucleotide probes on a microarray surface, were not well understood. We consider microarray technology as an instrument for measuring concentrations in multicomponent mixtures of DNA or RNA species. From this point of view, selectivity, response function and reproducibility must be known for appropriate analytics in real world applications. Other laboratories devised *ad hoc* approaches to make biological sense of microarray signals. These approaches have been extensively implemented and are now widely accepted in the published literature. Recent significant advancements in the understanding of nucleic acid hybridization and dissociation on microarray surfaces have revealed a number of inconsistencies between physical chemistry and the *ad hoc* approaches. The purpose of this mini-conference is three-fold: (i) to update developments in the understanding and application of microarrays, (ii) to identify and resolve inconsistencies in microarray analytics, and (iii) to discuss the future of microarray technology from the perspective of measuring principles and potential applications. We believe that this mini-conference is essential for moving forward microarray research and also for the advancement of new technologies such as 'next-generation' sequencing, which depend upon surface-hybridizations and array capture.

Objectives

1. Recognize contradictions in the theoretical foundation of hybridization-based technologies.
2. Identify gaps in factual experimental basis of the existing theories.
3. Suggest future experiments to fill up the gaps.
4. Prepare a collective review to a high-rank journal, such as Nature Methods or Science.

Participants

Name, address	Keywords	Refs
Binder, H. University of Leipzig, Germany binder@izbi.uni-leipzig.de	hook-calibration, Affymetrix, nonspecific hybridization, mismatch, SNP detection, sequence effects	4, 5, 6, 7, 8, 9, 10, 12, 18
Buhot, A. Institut Nanoscience et Cryogénie, France arnaud.buhot@cea.fr	hybridization isotherms, brush effects, thermodynamics, surface effects, spacers	21, 22, 26, 27, 28, 29, 30
Burden, C. The Australian National University, Australia conrad.burden@anu.edu.au	Langmuir models, analysis of spiked-in experiments, physic-chemistry of hybridization, statistics	11, 12, 13, 14
Carlon, E. Katolieke Universiteit Leuven, Belgium. enrico.carlon@fys.kuleuven.be	labeling, binding, thermodynamics, Affymetrix, mismatches, nearest neighbor, background subtraction, inverse Langmuir	15, 16, 20, 19, 34, 35, 36, 37, 45, 46, 56, 88
Grainger, D.W. University of Utah, USA david.grainger@utah.edu	array surface capture, surface chemistry	17, 23, 48, 89
Halperin, A. Université Joseph Fourier, France. ahalperin@cea.fr	hybridization isotherms, brush effects, thermodynamics, surface effects	26, 27, 28, 29, 30, 31
Harrison, A.P. harry@essex.ac.uk **Upton, G.** gupton@essex.ac.uk University of Essex, UK.	image processing, calibration, Affymetrix, probes, chimeric transcripts, probe sets, outliers	1, 2, 32, 33, 47, 53, 72, 74, 75, 78, 81, 82
Hooyberghs, J. VITO, Belgium jef.hooyberghs@vito.be	thermodynamic equilibrium, nearest neighbor model	36, 37
Kreil, D. Boku University Vienna, University of Cambridge David.Kreil@boku.ac.at	gene expression profiling, low-level data modelling, idenfication and removal of measurement artefacts, thermodynamic modelling for probe design and signal read-out, signal extraction and normalization	3, 41, 43, 44, 49, 55
Levicky, R. New York University, USA rlevicky@poly.edu	surface hybridization, complementary metal oxide semiconductor	24, 25, 39, 40, 42, 50, 51, 76, 77, 79, 80
Ott, A. Universität des Saarlandes, Germany albrecht.ott@physik.uni-saarland.de	surface hybridization, hybridization affinity, mismatches and base bulges	54, 57, 58, 59
Pettitt, B.M. University of Houston, USA. pettitt@uh.edu	surface effects, melting, surface electrostatic effects	38, 71, 85, 86, 87
Pozhitkov, A.E. Max-Planck Institute for Evolutionary Biology, Germany alexander.pozhitkov@evolbio.mpg.de **Noble, P.A.** Alabama State University, USA. panoble@washington.edu	competitive hybridization model, gel-pad oligonucleotide microarrays, probe design, oligonucleotide probes behavior, variability in melting, nonequilibrium thermal dissociation, stringent washing, quantification of multiple nucleic acid targets, nonspecific hybridization, hybridization isotherms, scanner calibration, nearest neighbor	52, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 73

Keywords by category

1. Array platforms and technologies, probes and targets

Microarray platforms: Affymetrix/Illumina/Agilent/ gel-pad oligonucleotide microarrays / electrochemical DNA detection / complementary metal oxide semiconductor (CMOS) / fluorescence detection / capacitive monitoring / X-ray photoelectron spectroscopy and infrared spectroscopy
Methods: quantification of multiple nucleic acid targets / SNP / gene expression
Spotting: maleimide-activated supports / dendrimer-mediated transfer printing
Targets: label-free DNA analysis / nucleic acid labeling / chimeric transcripts

2. Physico-Chemistry of hybridization and dissociation

Oligonucleotide probes behavior: outliers/ polyelectrolyte brushes/ brush effects / probe design / probe sets / spacers / surface electrostatic effects and hybridization on surfaces / thermodynamics / hybridization isotherms / hybridization affinity / binding affinities
Problems: nonspecific hybridization / mismatches / base bulges / experimental bias
Dissociation: nonequilibrium thermal dissociation / melting / stringent washing
Models: competitive hybridization model / inverse Langmuir / Langmuir model / nearest neighbor model / physicochemical modeling / sequence-specific calibration

3. Practical issues, applications and data analysis

Calibrations: scanner calibration / signal calibration / image processing / hook-calibration / background subtraction
Extracting primary characteristics, adequate preprocessings: expression (mRNA, miRNA, ncRNA), genotyping/copy numbers, methylation pattern
Quality control, error progression in data analysis

4. Perspectives

Are the arrays dead or what might be their niche of survival? Special arrays/applications (e.g., array capture for Next Generation sequencing); Physico-chemical challenges in next generation sequencing technologies

Tentative schedule of events

May 9th

Afternoon Arrival, Registration, and Welcome Remarks

May 10th

Morning Backgrounder with short introductions; 8 people 15 min talks (10 mins background + 5 minute discussion).

Noon Lunch provided

Afternoon Talks on new unpublished achievements.

Evening Dinner

May 11th

Morning Round table discussion on coherent theory and practice flaws. Actual problems and challenges, models and concepts, applications and perspectives. Development of independent cross-checks.

Noon Lunch provided

Afternoon Discussions of contradictions. Definition of subfields and key players. Interactions between theoreticians and experimenters. Does the surface affect hybridization/dissociation? How? What has to be done to understand it? Need for systematic evaluation? What is the experimental basis for the above question? Are there any experimental studies using AFM on what is happening on the surface?

Evening Dinner

May 12th

Morning Departure to the airport.

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