Chemosensation at the physical limit by sea urchin sperm

Inaugural-Dissertation

zur

Erlangung des Doktorgrades

der Mathematisch-Naturwissenschaftlichen Fakultät

der Universität zu Köln

vorgelegt von

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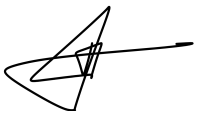
X  FEDIR LAVRYK

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Tag der mündlichen Prüfung:	10. Sept 2021

Abstract

Sperm from the Atlantic purple sea urchin *Arbacia punctulata* has become an attractive model for studying biological microswimmers and chemotaxis, primarily because of the ease of establishing chemotactic assays in controlled laboratory conditions. More than 100 years of research uncovered the molecular machinery that is responsible for chemosensation and guidance. The sensitivity of the sperm from *A. punctulata* reaches the limit of what is physically possible, they are able to detect single molecules of the species-specific chemoattractant released by eggs of the same species.

Previous studies have investigated sperm signalling at the stimulus level of single to few chemoattractant molecules. These experiments made use of rapid kinetics techniques that provide measurement averages across a large ensemble of sperm cells. While providing valuable insights, these studies are not best-suited to study an inherently stochastic problem. In this thesis, I study single sperm cells while stimulated with single quanta of excitation, i.e., single chemoattractant molecules or single molecules of secondary messenger. For this purpose, I exploit an opto-chemical method in which light is used for a targeted release of molecules.

The sperm chemoreceptor, guanylate cyclase, is known for its extraordinary supramolecular arrangement at the flagellar membrane in threads, as well as for negative cooperativity of attractant binding. In my Thesis, I study kinetics of the chemoattractant binding to the sperm guanylate cyclase. Using fluorescently labelled chemoattractant analogues, I determine the rate of attractant unbinding from the receptor at the flagellum. I also reconstruct the kinetic rates for a standalone chemoreceptor, as if it would not be biased by dense receptor clustering and diffusion-limited supply of the attractant. Furthermore, I collect additional evidence towards the hypothesis that the negative cooperativity of the receptor originates from its quaternary structure. Free Gibbs energy of attractant binding is estimated for the sperm guanylate cyclase from the frequency of spontaneous sperm activations.

The part of the signalling cascade of sperm chemotaxis that is downstream to the chemoreceptor is also studied by releasing single molecules of the secondary messenger directly inside of the sperm flagellum. Live-cell calcium fluorimetry is massively used to access the signalling state from hundreds of individual spermatozoa with high level of detail. I question the sensitivity of the sperm to cGMP release and prove that essentially stochastic mechanism determines latency of sperm responses to weak stimulations. A mechanism capable of explaining sometimes dramatic delays of sperm responses is proposed. The analysis of the sperm reactions to prolonged and periodically modulated stimuli suggests the presence of an adaptability mechanism in the transduction cascade.

Based on these insights, I discuss the physiological relevance of the ultra-sensitivity achieved by sperm. Using digital inline holographic microscopy, I collect trajectories of the sperm swimming far from walls before and after weak stimulation by the secondary messenger. The behavioural responses that I observe suggest that sperm might switch to a different behavioural mode upon binding of a single molecule of the attractant, which presumably primes the active chemotaxis.

Up to today, only a handful of model systems have been shown capable of responding to single molecules. This study advances us into understanding how the chemotactic signalling pathways operate at the physical limit. Furthermore, these insights might prove useful in microswimmer designs for application in science and industry.

Zusammenfassung

Spermien sind evolutionär für die Bewegung und Navigation von Nutzlast optimiert. Daher werden sie als vielversprechende Grundlage für die Entwicklung von extern kontrollierten Nanorobotern betrachtet. Spermien des Lila Seeigels *Arbacia punctulata* sind seit Jahrzehnten ein interessantes Modell für die Erfoschung biologischer Mikroschwimmer und Chemotaxis, da chemotaktische Proben mit geringem Aufwand unter Laborbedingungen entnommen werden können. Mehr als 100 Jahre Forschung haben die molekularen Vorgänge aufgeklärt, die für die Chemosensation und Navigation der Spermien verantwortlich sind. Ferner wurde gezeigt, dass die Spermien von *A. punctulata* die Grenzen des physisch Möglichen erreichen: diese sind in der Lage, einzelne Moleküle des Lockstoffs zu erkennen, die von den Eiern ihrer Spezies abgesondert werden. Allerdings wurden noch nicht alle Mechanismen der Signalkaskade, die die Chemotaxis der Spermien erhält, in allen Details entschlüsselt.

Ich untersuche den Lockstoffbindungsprozess des Spermiumrezeptors bezüglich der physikalischen und chemischen Kinetik. Der Chemorezeptor des Spermiums, die Guanylatzyklase, ist für herausragende Affinität zum Lockstoff aber auch für seine außergewöhnliche supramolekulare Anordnung an der Flagellarmembrane in Fäden bekannt, ferner außerdem für seine negative Kooperativität der Lockstoffbindung. Unter Benutzung fluoreszenzmarkierter Lockstoff-nachbildungen stelle ich die Reaktionsratenkonstante für den Lockstoff-Rezeptor-Komplex fest. Ferner bringe ich einen weiteren Nachweis dessen, dass die negative Kooperativität des Rezeptors ausschließlich von seiner Quartärstruktur stammt. Die freie Gibbs-Energie der Lockstoffbindung für die Guanylatzyklase des Spermiums schätzte ich ab.

Darüber hinaus untersuche ich die Spermien des Seeigels intensiv auf der Ebene einzelner Zellen, um neue Erkenntnisse über die chemotaktische Signalisierung zu gewinnen. Dabei findet eine optochemische Methode Anwendung, in der Licht für die gezielte Freisetzung des sekundären Botenstoffes innerhalb der Spermiengeißel genutzt wird. Dieses Vorgehen erlaubt die Messung der Signalkaskade des Spermiums bei Umgehung des Chemorezeptors. Mittels Calciumfluorometrie von sich schnell bewegenden Spermien und der opto-chemischen Methode zeige ich, dass die Botenstoff-abhängige Phase der Signaltransdukzion weitgehend stochastisch ist. Ich analysiere die Spermienreaktionen zu andauernden und periodisch modulierten Stimulationen und zeige damit die Existenz eines Adaptierungsmechanismus in der Transduktionskaskade an. Diese erhält die Anpassung des dynamischen Bereichs der Chemosensation passend zu den Bedingungen in denen sich das Spermium bewegen muss.

Ausgehend von diesen Erkenntnissen diskutiere ich die physiologische Relevanz der Ultrasensitivität für das Spermium. Unter Benutzung von holographischer Mikroskopie habe ich Pfade der Spermien-bewegung weit entfernt von Hindernissen vor und nach leichter Pulsstimulation durch den sekundären Boten aufgezeichnet. Anzeichen einer Entscheidungsfindung oder eines multi-modalen Verhaltens der Spermien erlauben die Hypothese, dass die Antwort des Spermiums auf ein einzelnes Molekül eine Verhaltenssteuerung ist, die die Wahrscheinlichkeit der Fortpflanzung erhöht. Diese Studie vertieft das Verständnis der chemotaktischen Signalkaskade des Spermiums des Seeigels, was für die externe Kontrolle der Spermienmobilität essentiell ist, und dient damit der Weiterent-wicklung von künstlichen Mikroschwimmern für Forschung und Industrie.

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1. Introduction

1.1. Preface

Sperm belong to what is called “active matter” because they perform a mass transfer in a directed, non-entropic manner without the need for continuous external control. Moreover, sperm are capable of detecting the lowest amount of stimulation physically possible – a single molecule, and of deciding about a gradient direction having sampled only a few hundred attractant molecules[1,2]. In this work, I assess in quantitative terms the chemosensory signalling in sea urchin sperm that achieves deterministic chemotaxis and exquisite sensitivity to the chemoattractant.

Sperm is among the most referred prospective components for nanorobotics[3] because it is designed to propel, navigate, and deliver cargo, and appears evolutionarily optimal in that role[4]. Being assembled exclusively from biomolecules, sperm are probably the most biocompatible among other candidates for applications in nanomedicine. Swarms of sperm from some species demonstrate emergent behaviour[5–9]. Sea urchin sperm is especially prominent: it does not feature heteromorphism[10], and the population of sea urchin sperm is thought to be homogenous[11]. Evidence of emergent behaviour in sea urchin sperm exists[12,13]. Additionally, there are indications that sea urchin sperm exhibit some multimodal behaviour to stimuli of various nature, i.e., has a set of distinctive motility patterns[14–16]. The trajectory of *Arbacia punctulata* sperm loaded with caged cGMP can be influenced in a deterministic way using light[17]. The chemosensory signalling pathway of the *A. punctulata* sperm features a sensory-motor loop that allows maintaining reliable chemotaxis even upon a shift of environmental properties or in case of major deviations of sperm swimming velocity.

The knowledge about how sperm is guided, how reliable chemical cues are in complex hydrodynamic media, and how sperm optimize chemotaxis performance by implementing particular strategies is essential for the development of a microswimmer suitable for medical or industrial uses. These topics are broadly covered in the present work. Understanding the abilities and limits of chemosensation and chemotaxis are essential for many fields of applied and fundamental science. Noisy or precise, deterministic or biased-random – in either form, it is relevant for ecology and population biology (nutrient scavenging, mating), biophysics (signal transduction), molecular biology (gene regulation, cell division), developmental biology (embryonic development)[18–21].

Being in essence fundamental research, this Thesis aims at advancing the knowledge on the navigation of sperm from external fertilizers, with conceptual or practical findings and hypotheses applicable for diverse problems of biophysics, biosensorics, ecology, and physics of behaviour, and has several potential applications. The work utilizes a novel concept of reverse opto-chemical engineering (ROCE) that has a large potential as a tool for biophysical studies. ROCE provides several methodologic and conceptual clues useful for an assessment of single-quanta sensitive sensory systems with stochasticity (Hamzeh et al., in prep). Chemists may find the evidence of a solvent-dependent extinction coefficient shift in a coumaryl-caged compound worth attention. Search strategies are of importance for population biology and information theory, and the issues of molecular noise and single-quanta sensitivity are relevant for statistical physics and communications.

Though a common understanding of microscopy techniques, digital imaging, microfluidics, hydrodynamics, mathematical statistics and signal processing theory will simplify the reading, I aimed at providing a sufficient introduction where necessary, supplementing it with simple, mostly

Abbreviations used in text

Acronym	Meaning	Reference Chapter (if applicable)
$[Ca^{2+}]_i$	intraflagellar Ca^{2+} concentration	1.2.2
2D	two-dimensional; flat	1.2.3
3D	three dimensions; unconfined	1.2.3
-AM	acetoxymethyl ester	2.2.3
ASW	artificial seawater	2.2.2
ATP	adenosine triphosphate	1.2.3
BNC	Bayonet Neill–Concelman type connector	2.3
c. v.	coefficient of variation	1.2.5
cAMP	cyclic adenosine monophosphate	1.2.4
CatSper	sperm-specific Ca^{2+} channel	1.2.4
CCD	charge-coupled device	2.3.1
CCDF	CDF complement	S.3.1
CDF	cumulative distribution function	S.3.1
cGMP	cyclic guanosine monophosphate	1.2.4, 1.2.5
CMOS	complementary metal oxide semiconductor	2.7.1
CNBD	cyclic nucleotide-binding domain	1.2.4
CNGK	K^+ selective cyclic nucleotide-gated channel	1.2.4
CPC	central pair complex	1.2.2
DEACM#	coumaryl-caged compound	2.2.4
DEACM-OH	coumaryl alcohol	2.5.2
DIHM	digital inline holographic microscopy	2.3.7
DLP	the micromechanical mirror array device	2.5
DMNB#	4,5-Dimethoxy-2-nitrobenzyl-caged compound	2.3.3, 1.2.1
DMSO	dimethyl sulfoxide	2.2.1
DMT	doublet microtubules	1.2.2
DRC	dynein regulatory complex	1.2.2
EC_{50}	half-maximal effective concentration	2.2.5
EDTA	ethylenediaminetetraacetic acid	2.2.1

FACS	fluorescence-assisted/activated cell sorting	2.7.2
flR	fluorescent resact alnalog	2.2.5
FOV	field of view	2.3.1
FPS	framerate unit (frames per second)	2.3.1
GAFa	guanylyl/adenylyl-phosphate binding domain	3.3.4
GC	guanylate cyclase	1.2.4
GFP	green fluorescent protein	2.2.3
G_α, G_β, G_γ	α, β, γ-subunits of transducin	1.2.5
HCN	hyperpolarization-activated CNG channel	1.2.4
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid	2.2.1
HPFA	perfluoroalkoxy-based polymer similar to Teflon	2.3.4
LED	light emission diode	2.3.2
LLE	Lumencor light engine	2.3.1
LR	(fluorescent) N-Ac-N-DEACM-resact	2.2.5
MSD	mean-squared displacement/deviation	1.2.1, S.1.2
NCKX	$Na^+/Ca^{2+}/K^+$ eXchangers	1.2.4
ND	milky (neutral density) light filter	2.3.3
PBS	phosphate buffer saline	2.2.1
PC	personal computer	
PDE	phosphodiesterase	1.2.4
PDE5	phosphodiesterase type 5	3.3.4
PDF	probability density function	S.3.4
PEG	polyethylene glycol	2.7.1
pH_i	intraflagellar acidity (alkility)	1.2.4
PLL	poly-L-lysine	2.7.1
PMCA	plasma membrane Ca^{2+} ATPases	1.2.4
rcf	relative centrifugal force, g-force	1.1.1
Rh*	activated rhodopsin	1.2.5
RMSD	root mean square displacement/deviation	1.2.1, S.1.2
ROCE	reverse opto-chemical engineering	1.1
RR	(regular unmodified) resact	2.2.5

S. D.	standard deviation	
sACY	soluble adenylyl cyclase of type γ	1.2.4
sNHE	sperm-specific sodium-proton exchanger	1.2.4
TIRF	total internal reflection fluorescence	2.7.1
UV	ultraviolet	2.2.4
VAP	average path velocity	1.2.3
VCL	curvilinear velocity	1.2.3
V_m	membrane voltage	1.2.4
VSL	straight-line velocity	1.2.3
v/v	volume-to-volume (for mixture proportions)	2.6.2

Trademarks designation is omitted in the text.

List of figures

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List of used literature

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Acknowledgements

I would like to express my highest gratitude to all people who supported and guided me during the preparation of the Thesis all around, especially to my direct supervisor, Dr Luis Alvarez, and my scientific advisor, Prof Dr U. Benjamin Kaupp. Plenty of ideas were born in intensive and delightful scientific discussions with them and with Dr An Gong, Dr René Pascal, Dr Jan Jikeli, Dr Hussein Hamzeh, Anastasiia Priss, Michelina Kierzek, Volodymyr Korsuns'kyj. I thank all my colleagues and collaborators at the research center caesar in Bonn, in Forschungszentrum Jülich as well as in Technische Universität Dresden for the fruitful discussions and productive exchange of thoughts and ideas. I regard all current and former members of MNS Department at caesar for the friendly working atmosphere, scientific seminars, useful discussions, and beautiful time we spent together.

I also want to acknowledge other people and institutions that made this research possible at either stage, above all – Prof Dr Berenike Maier and Prof Dr Carsten Fallnich for their patronage, the Foundation caesar, the University of Cologne (STIBET), DFG, and DAAD for having supported this research financially, and to research center caesar in Bonn, CERA at UKM/WWU Münster, the Marine Lab in Woods Hole, and the Florida State University in Tallahassee for providing access to their facilities and equipment, and for the efforts invested in favour of the presented project. I also regard Rolf Honnef and his colleagues from the Workshops of the research center Caesar for their passion for manufacturing the best possible customized tools for my research.

I honour Dr Leonid Ryvkin, Dr Kseniia Afitska, Dr Liudmila Masliuk, and Iryna Lavryk for their immense help in proofreading and correction the text and the figures of this Thesis. I also thank to Martin and Jelena Mory for their support in preparing German pieces of this Thesis as well as for making my stay in Germany much more comfortable than it could have been without their help.

Finally, I would like to express my gratitude to Heike Krause, Lisa Brüning, Olesya and Yevhen Priss, Dr Volodymyr Shvadchak, Roman and Kateryna Lavryk, Mariia Ihnatenko, and Christina Wetzels for all-round organisational support that is impossible to overemphasize. Without their help, the work could have been delayed inevitable.

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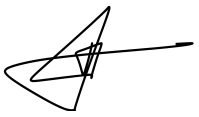
X 

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