

# The computational sperm cell

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**Sperm are guided to the egg by a gradient of chemical attractants – a process called chemotaxis. The binding of the chemoattractant to receptors on the surface of the flagellum triggers a cascade of signaling events that eventually lead to an influx of Ca<sup>2+</sup> ions. Based on these Ca<sup>2+</sup> surges, which control the waveform of the flagellar beat, sperm adjust their swimming path toward the egg. In past years, many components of chemotactic signaling have been identified. Moreover, kinetic spectroscopy and imaging techniques unraveled the sequence of cellular events controlling swimming behavior. During navigation in a chemical gradient, sperm perform a surprising variety of computational operations. Here we discuss theoretical concepts of navigation strategies and the cellular underpinnings.**

## Sperm: fertilizing biomachines

Egg and sperm must meet for fertilization and, while on this journey, sperm perform some impressive navigational feats. A beating tail, called flagellum, propels sperm toward the egg. In both mammals and invertebrates, sperm use various sensing mechanisms to gather physical or chemical cues to spot the egg.

In mammals, three different mechanisms have been proposed to guide sperm through the narrow oviduct: chemotaxis [1,2], thermotaxis [3], and rheotaxis [4,5] (see Glossary). Neither of these mechanisms or their contribution (if at all) to sperm guidance is well understood. This lack of understanding may be due to the inability to emulate the complex native conditions that mammalian sperm encounter during fertilization. On their journey, mammalian sperm pass through two processes – capacitation and hyperactivation – to acquire the potential to fertilize the egg [1,6]. At any given time, only a fraction of sperm is capacitated or hyperactive; therefore, mammalian sperm populations are heterogeneous. Moreover, mammalian sperm are spatially constrained in the anisotropic female reproductive tract. In addition, they interact with the ciliated epithelial layer that lines the oviduct.

By contrast, so-called broadcast spawners, mostly marine invertebrates, release their gametes into the water, where

sperm swim freely. 2D and 3D swimming of sperm in aqueous medium can be emulated in the laboratory with reasonable precision [7–10]. Importantly, complex maturation processes observed in mammalian sperm are absent in their invertebrate counterparts. Furthermore, these sperm populations are homogeneous. Because of their simpler nature, sperm from sea urchins have served as the model system for the study of fertilization for more than 100 years [11]. Using this model, the process of chemotaxis has been firmly established and the corresponding chemoattractants – small peptides – have been identified. Chemical tools and rapid kinetic techniques have been developed (e.g., caged chemoattractants [12–15] and caged cyclic nucleotides [16,17]) to decipher the navigation strategy in a chemical gradient and to delineate the sequence of signaling events occurring in sea urchin sperm (Box 1). This pathway endows sperm with exquisite sensitivity: they can register the binding of a single molecule of chemoattractant and transduce it into a cellular response.

Here we review the signaling and navigation mechanisms sperm use during fertilization with an emphasis on sea urchin sperm. We discuss how sperm detect and count single molecules, how they integrate multiple binding events while cruising in a chemical gradient, and how they translate chemoattractant binding into a change in flagellar beat and, thereby, swimming path. We also highlight commonalities and differences between sea urchin and mammalian sperm.

## Hydrodynamics and swimming patterns

### *Sperm swim near surfaces*

The motion of microswimmers like sperm, bacteria, and algae is ruled by the hydrodynamics of the embedding fluid and encaging compartment (Box 2). During internal fertilization, mammalian sperm swim along the narrow oviduct and interact with the epithelium. Moreover, sperm from some broadcast spawners, such as fish, swim on the surface of the large egg during their search for the small entrance to the fertilization site, known as the micropyle [18]. Thus,

## Glossary

**Capacitation:** a set of mechanisms by which mammalian sperm acquire the capability to fertilize the egg.

**Chemotaxis, rheotaxis, and thermotaxis:** refer to the directed movement of a microswimmer in a gradient of a chemical substance (chemoattractant), flow velocity, or temperature, respectively.

**Hyperactivation:** sperm motility mode characterized by a vigorous whiplash beat of the flagellum.

**Microswimmers:** cells, small organisms, and artificial swimmers of micrometer scale that swim at low Reynolds numbers ( $Re \leq 1$ ).

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### Box 1. The chemotactic signaling pathway

The study of chemotactic signaling in sperm is primarily delineated in the sea urchin *Arbacia punctulata* (Figure 1). The binding of chemoattractant molecules triggers a sequence of biochemical and electrical events that eventually open  $\text{Ca}^{2+}$  channels in the membrane. The ensuing  $\text{Ca}^{2+}$  entry into the flagellum changes the flagellar beat. First, the chemoattractant peptide resact [77] binds to a receptor-type GC [78–80] and stimulates rapid cGMP synthesis [12]. The rapid surge of cGMP activates  $\text{K}^+$ -selective cyclic nucleotide-gated (CNG) ion channels, followed by a transient hyperpolarization of the cell [59,81,82]. The hyperpolarization activates two additional signaling components: a sodium/proton exchanger (NHE) [83,84] and a hyperpolarization-activated CNG (HCN) channel [85]. The NHE activity causes rapid intracellular alkalinization, whereas on opening of HCN channels  $\text{Na}^+$  flows into the cell. During the ensuing depolarization, voltage-dependent  $\text{Ca}^{2+}$  ( $\text{Ca}_v$ ) channels open. During

recovery from stimulation, the resting  $[\text{Ca}^{2+}]_i$  and cGMP level are restored. A  $\text{Na}^+/\text{Ca}^{2+}/\text{K}^+$  exchanger (NCKX) [86] and a CaATPase [87] export  $\text{Ca}^{2+}$  from the cell, whereas a phosphodiesterase (PDE) removes cGMP by hydrolysis [88]. Although the function of cGMP is well established, the role of cAMP remains vague. cAMP is probably exclusively synthesized by a sAC [89]; the sAC, at least in mouse sperm, seems to be associated with the NHE [90]. Direct targets of cAMP are the HCN channel and the NHE itself, which – surprisingly – harbors a characteristic binding site for cyclic nucleotides. When sperm approach the egg, they adapt to the ever-increasing resact concentration. The underlying mechanisms are unknown, but downregulation of GC activity might be one mechanism [40]. A similar signaling pathway in ciliary photoreceptors transforms the absorption of a single photon into a small hyperpolarization of  $\sim 1$  mV [2].

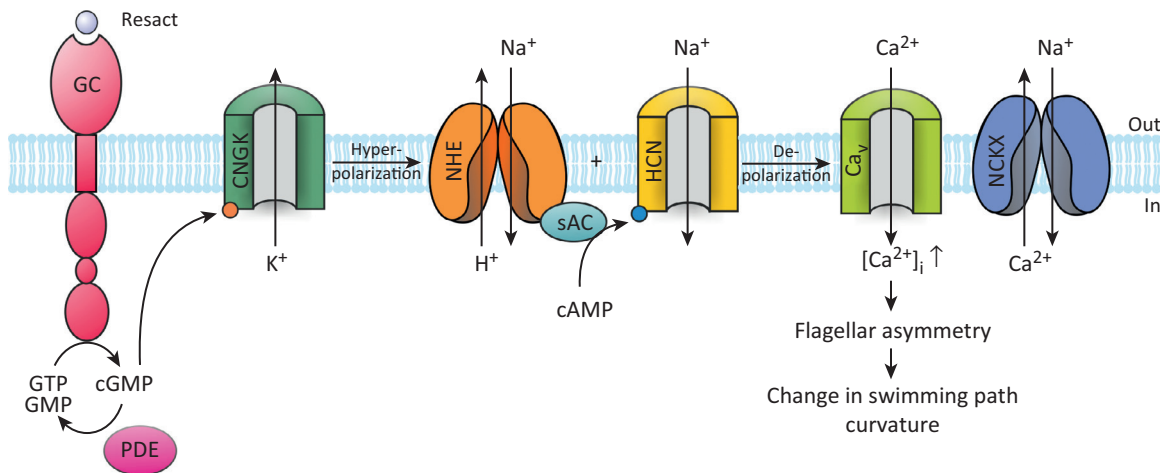


Figure 1. Chemotactic signaling pathway for sperm of the sea urchin *Arbacia punctulata*.

the interaction of sperm with boundaries is important during fertilization. From a hydrodynamics viewpoint, sperm can be classified as pushers; that is, microswimmers with a motor in the back (the flagellum) and a passive load at the front (the head) [19,20]. The flow field around a pusher is characterized by a backward flow in the rear (because the flagellum pushes the liquid backwards) and a forward flow in the front (because the head is dragging along fluid). The expelled fluid must be replenished by a flow from the side (Figure 1A). When a pusher comes close to a wall, the flow field becomes distorted. Because the pulling in of fluid is hindered from the side of the wall, the fluid is mostly replenished from the opposite side, pushing the cell toward the wall. If the pusher swims parallel to a wall at a distance ( $z$ ) much larger than the swimmer size ('far-field approximation'), it drifts toward the wall with a velocity  $v(z) = P/(32\pi\eta z^2)$ , where  $P$  is the dipole strength, which is determined by the length of the microswimmer and beating activity [21]. As sperm approach a wall, additional interactions initiate and the far-field approximation fails. Numerical approaches using particle-based meso-scale hydrodynamics show that sperm become attracted to the wall and the beating plane of the flagellum aligns with the wall (Figure 1B,C and Video S1 in the supplementary material online) [22]. However, the parallel alignment is not perfect: sperm swim with their long axis

slightly inclined, which pushes the head against the wall, further stabilizing sperm at the wall [23]. This tilt results from either the divergent flow field at the end of the flagellum or the steric repulsion between the beating flagellum and the wall [24]. In microchannels, sperm also swim against rather than near the wall [24,25], consistent with results from mesoscale simulations [22] but at odds with the near-wall swimming predicted by other computational approaches [26]. In conclusion, hydrodynamic interactions provide a theoretical framework that explains why sperm accumulate at interfaces [27–29], follow boundaries in microchannels [25], and stay at the egg surface for some time.

#### Sperm swim on looping paths controlled by $\text{Ca}^{2+}$

$\text{Ca}^{2+}$  controls the beat of many flagella or cilia; for example, in airway epithelia, *Chlamydomonas*, and *Paramecium* [30–33]. Sperm are no exception: chemotactic steering also requires  $\text{Ca}^{2+}$  [34]. Novel photonic techniques and chemical tools allow recording of  $\text{Ca}^{2+}$  signals and the simultaneous tracking of single sperm from marine invertebrates navigating in a gradient [10,35–37]. These methods have greatly advanced our understanding of chemotactic navigation.

Most importantly, sperm swim on periodic paths by design [38]. Near a surface, sperm from sea urchin, starfish, and tunicates swim in small circles with a frequency of

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