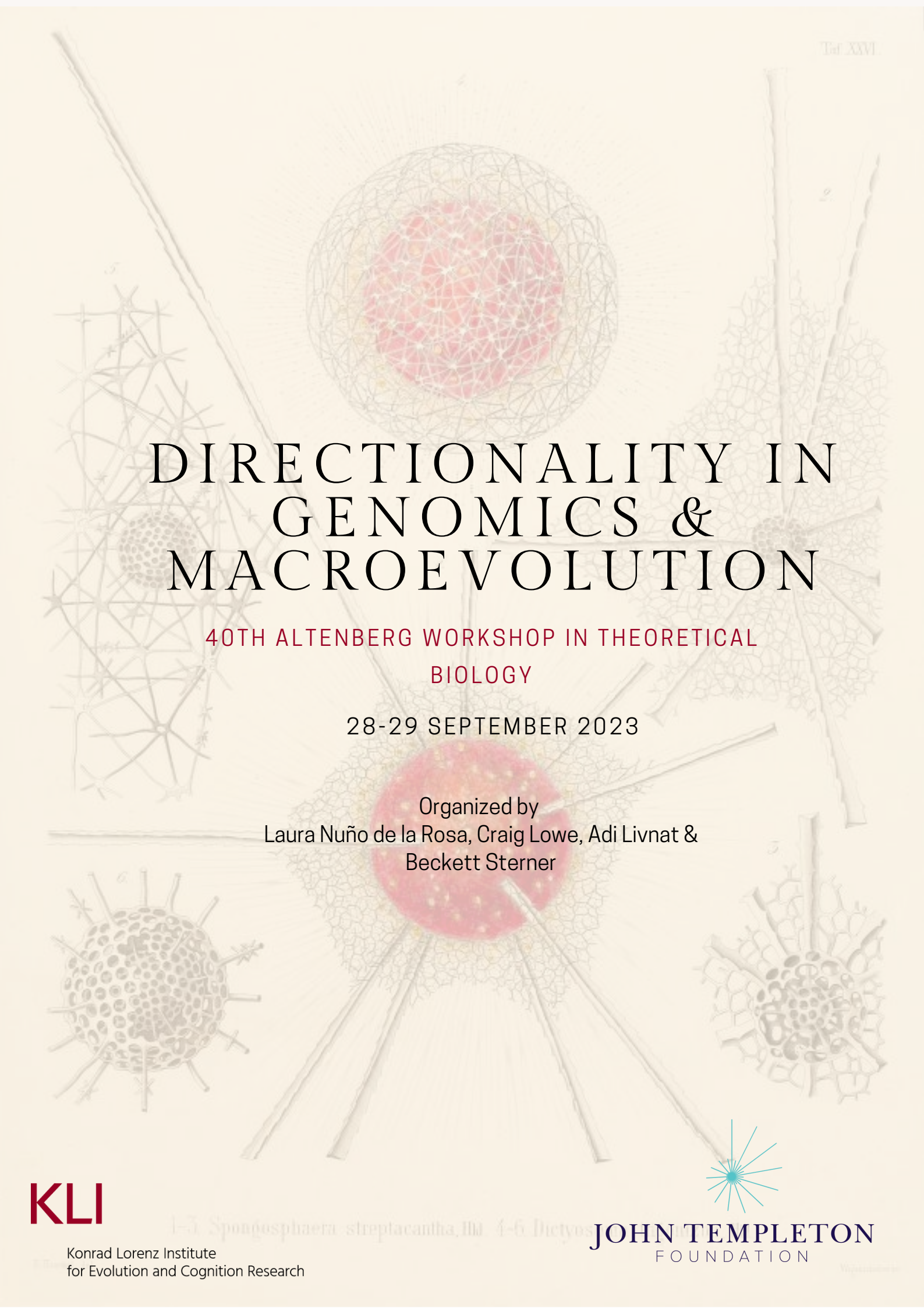

DIRECTIONALITY IN GENOMICS & MACROEVOLUTION

40TH ALTENBERG WORKSHOP IN THEORETICAL BIOLOGY

28-29 SEPTEMBER 2023

Organized by
Laura Nuño de la Rosa, Craig Lowe, Adi Livnat &
Beckett Sterner

KLI
Konrad Lorenz Institute
for Evolution and Cognition Research

JOHN TEMPLETON
FOUNDATION

WELCOME

to the 40th Altenberg Workshop in Theoretical Biology. The Altenberg Workshops are interdisciplinary meetings organized by the KLI in Klosterneuburg, Austria. The workshop themes are selected for their potential impact on the advancement of biological theory. Leading experts in their fields are asked to invite a group of internationally recognized scientists for three days of open discussion in a relaxed atmosphere. By this procedure the KLI intends to generate new conceptual advances and research initiatives in the biosciences. We are delighted that you are able to participate in this workshop, and we wish you a productive and enjoyable stay.

GERD B. MÜLLER, PRESIDENT

THE TOPIC

Detecting biases in biological patterns and processes is central to life science inquiry. However, since unambiguous signatures of directionality are often elusive, it is also a source of methodological frustration. Increasingly sophisticated experimental and theoretical tools have been utilized in the areas of genomics, phylogenetics, and evolutionary paleobiology. Nevertheless, new statistical models and model systems are required to isolate signals from noise in large data sets. Concerted efforts by multidisciplinary teams working on the details of mutational processes, genomic signatures, and macroevolutionary trends help to orient future research with robust procedures that identify directionality in lineages, thereby advancing our understanding of evolutionary dynamics within and across populations and lineages.

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THE WORKSHOP

The workshop on Directionality in Genomics and Macroevolution will convene 16 researchers over two days to explore innovative conceptual and methodological approaches for detecting and explaining evolutionary trends. Of these participants, 11 are involved in the three projects of the Cluster 'Directionality in Genomics and Macroevolution,' part of the cohort program 'Agency, Directionality, and Function,' funded by the John Templeton Foundation. These projects are coordinated by Laura Nuño de la Rosa and include 'The genetic basis of macroevolutionary trends,' led by Craig Lowe; 'Mutation rates, variational specificity, and genomic directionality,' under the direction of Adi Livnat; and 'New tests of directionality in fossil lineages,' coordinated by Beckett Sterner. We are also honored to have Melanie Hopkins, Gene Hunt, John Matick, Gerd Müller, and Günter Wagner as invited commentators, serving as scientific advisors to the Cluster.

The aim of the workshop is to discuss the results achieved in each project within a shared theoretical framework, address transversal conceptual issues linking our cluster to other clusters of the cohort program, and explore future collaborations among members of the cluster, other participants of the cohort program, and external collaborators.

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THE WORKSHOP

The workshop will be structured into three thematic sessions, each devoted to one of the three projects, and a general discussion session. During the thematic sessions, the Principal Investigators (PIs) and project members will present the results of each project. Following each presentation, the external collaborators will offer their comments and feedback based on the presentation and the associated readings.

Each external commentator is assigned to coordinate the discussion time of their respective thematic session. The Discussion section will be structured around the following questions, which will serve as well as a framework for the discussions during the workshop:

- What do you think are the big questions to address in evolutionary biology? How do these projects contribute to solving these questions?
- What are the general questions/ideas across the three projects?
- Which new research questions/experiments on evolutionary rates and Directionality do you think should be pursued in the next 5 years?
- How to get the field of evolutionary biology interested in these new questions? What do you think are the core barriers in this regard and how do you think they can be overcome?
- How do you think the link between micro and macro directionality should be investigated?

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DIRECTIONALITY GENOMICS & MACROEVOLUTION

PROGRAM

28TH SEPTEMBER

THE GENETIC BASIS OF MACROEVOLUTIONARY TRENDS

CHAIR: JOHN MATTICK

9.30 am – 11.00 am	Presentations: Craig Lowe, Christiana Fauci, Riley Mangan
11.00 am – 11.30 am	Coffee
11.30 am – 12:30 pm	Discussion
12:30 pm – 2.30 pm	Lunch at the KLI

DYNAMIC LINEAR MODELING TO UNLOCK NEW TESTS OF DIRECTIONALITY IN FOSSIL LINEAGES

CHAIRS: CHAIRS: GENE HUNT & MELANIE HOPKINS

2.30 pm – 4.00 pm	Presentations: Beckett Sterner, Antonio Campbell, John Fricks
4.00 pm – 4:30 pm	Coffee
4.30 pm – 6.00 pm	Discussion
6.30 pm	Departure for Dinner at a Viennese Heurigen

PROGRAM

29TH SEPTEMBER

MUTATION RATES, VARIATIONAL SPECIFICITY, AND LONG-TERM DIRECTIONALITY IN GENOME EVOLUTION

CHAIR: GUNTER WAGNER

9.30 am – 11.00 am	Presentations: Adi Livnat, Dorit Fink-Barkai, Evgeni Bolotin, Daniel Melamed
11.00 am – 11.30 am	Coffee
11.30 am – 12:30 pm	Discussion
12:30 pm – 2.30 pm	Lunch at the KLI

GENERAL DISCUSSION

CHAIR: GERD MÜLLER

2.30 pm – 4.00 pm	Discussion
4.00 pm – 4:30 pm	Coffee
4.30 pm – 6.00 pm	Discussion
6.30 pm	Dinner at the KLI

DIRECTIONALITY GENOMICS & MACROEVOLUTION

ABSTRACTS

THE GENETIC BASIS OF MACROEVOLUTIONARY TRENDS

PI: CRAIG LOWE

Each morphological change observed in the fossil record is the result of one or more genomic changes within a gene or regulatory element. We are working to understand if three sequential periods of gene regulatory evolution that we previously identified on the lineage from the vertebrate ancestor to present-day humans, are in fact shared by all vertebrate lineages and represent a consistent progression for how complex life evolves at the molecular level. We are also working to assess the accuracy of our computational methods to infer ancestral genomic sequences by understanding the function of these inferred ancestral sequences and compare this functional readout to known functions.

Three Periods of Molecular Evolution

In a previous study, we identified millions of functional elements in the human genome and inferred when each originated. This resulted in us discovering three macroevolutionary molecular epochs (Lowe et al., 2011). These epochs extend from our vertebrate ancestor to present-day humans and are defined by a specific functional group of genes that was used for adaptation during that epoch. In the first epoch, key developmental genes had their expression patterns refined in early vertebrates, through the time when tetrapods first came onto land and greatly changed their body plan. The second and third periods showed progressively finer refinements of forms as genes involved in signaling between cells and then signaling within a cell were refined up to the present day. We discovered the three periods of regulatory evolution because of two innovations in our method, one theoretical and one technical. Our theoretical innovation was that while changing the set of genes that an organism possesses is important, previous studies have shown that the set of regulatory elements that control when and where these genes are expressed is more often the basis of adaptation (Carroll, 2005, 2008). For this reason, while previous studies had timed the creation of genes (Domazet-Loso et al., 2007; Domazet-Loso and Tautz, 2010), we timed the creation of both genes and their regulatory elements. Genes tended to be ancient, but regulatory elements explained the emergence of specific traits, such as body hair appearing in ancient mammals, as well as showed successive waves of genome-wide innovation (Lowe et al., 2011). Our technical innovation was an increased accuracy in timing when genomic regions originated. Previous studies used BLAST on the protein sequences of genes in isolation, which ignores genomic context such as the position of introns and the context of neighboring genes (Domazet-Loso et al., 2007; Domazet-Loso and Tautz, 2010). Others have published on how this older approach of only looking at protein sequences can often lead to inaccuracies and biases in the results (Moyers and Zhang, 2015). Our method, being genome-wide and at the level of DNA rather than proteins, is more accurate due to using the larger genomic context when identifying if another species has an orthologous genomic region, be it a gene or a regulatory element.

THE GENETIC BASIS OF MACROEVOLUTIONARY TRENDS

PI: CRAIG LOWE

Repeated Trends in the Evolution of Complex Life?

We have preliminary evidence that the genomic epochs are surprisingly consistent between vertebrate lineages. At the time, fish were the only part of the vertebrate tree with enough genomes to analyze a long lineage independent from humans. A part of this work that has consistently occupied our thoughts since its publication is that fish and mammals appear synchronized, even after their lineages split. Both fish and mammals continued refining the expression of key developmental genes for another 300 million years after their lineages diverged. Even more unexpected is that fish and mammals independently began the second epoch of refining the expression of their intercellular signaling genes and this epoch too ended at the same time (Lowe et al., 2011). We do not believe that this synchronization is an artifact of our methods, but we do not yet know what is causing it or if we will witness it in all vertebrates. As a core aim of this work we will test the hypothesis that this consistency between the progression seen in mammals and fish is not a coincidence, but rather a universal rule for the progression of gene sets that are successively optimized as a vertebrate evolves. We will perform a more detailed analysis with the hundreds of vertebrate genomes that are now available (Genereux et al., 2020), which will allow us to identify more functional elements, more accurately date their origin, and include additional lineages, such as amphibians, birds, and lizards. There are now sufficient genomes to definitively test the hypothesis that the first two epochs are shared between all major vertebrate lineages and define a set progression of how complex life evolves.

Are Primates Unique?

At the time we published the discovery of the three periods of regulatory evolution, there was no way to identify recently evolved functional elements on any lineage other than humans, due to a sparse sequencing of non-primate genomes. Due to this previous constraint, we do not currently know if the third epoch of gene regulatory innovation is specific to recent human evolution, or if it will also be observed in other lineages. We will assess each major vertebrate lineage for the presence of this third epoch to test if humans and other primates have moved on to a third period of regulatory evolution that is not observed in other vertebrates.

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STATE SPACE MODELING TO UNLOCK NEW TESTS OF DIRECTIONALITY IN FOSSIL LINEAGES

PI: BECKETT STERNER

Documenting temporal patterns in the existence and traits of evolutionary lineages provides the basic phenomena of evolutionary biology, and thus is essential to advancing our knowledge of the history of life. A crucial result in this respect has been that evolutionary lineages, like many other types of biological systems, exhibit a complex mosaic of randomness, sensitivity, and robustness in their dynamics with respect to changes in their environments (Hopkins and Lidgard 2012). Understanding the reasons for these dynamics leads to important explanatory questions at three compositional levels: what explains 1) the temporal behavior we observe for an individual trait of a lineage, 2) the mosaic of behaviors we observe among the set of traits of a lineage over time, and 3) the correlation or independence of traits we observe among taxonomic or ecological groups of lineages? Crucially, we expect the explanations at each of these levels to be connected as a result of causal relationships linking processes across scales.

Our project advances the mathematical modeling frameworks available for biologists to address these questions using time series data of species' phenotypic traits measured in sequences of fossil populations in successive sedimentary layers from a given locality (Gould and Eldredge 1977; Gingerich 1985). These time series provide an invaluable window onto the history of life for the purposes of documenting patterns of directional change and explaining the causes of these patterns in terms of driven processes such as natural selection toward a fitness peak or passive processes such as genetic drift (Turner and Havstad 2019). Many empirical studies, for example, have examined the relationship between body size and climatic temperature or whether shape variation in species' morphologies can be decomposed into distinct anatomical or developmental modules (Liow and Taylor 2019; Stuart et al. 2020). In addition, major theoretical debates hinge on what modes of individual trait evolution should be dominant in the evolutionary record, e.g. gradual directional change or stasis punctuated by short periods of rapid evolution, and how the rates and modes of trait evolution should be coupled to other biological processes such as organismal development, speciation, and ecological community assembly (Uyeda et al. 2011; Pennell et al. 2014; Hunt and Slater 2016).

However, existing modeling frameworks have important limitations in their ability to analyze dependencies among multiple traits and environmental variables simultaneously and make maximal use of multiple specimens drawn from populations at a time point. The state space modeling framework can fill this gap by providing an accessible modeling framework for paleobiologists with a wide range of advantages for model estimation, validation, and analysis. While state space models are an established, widely used approach to statistical modeling of time series (Shumway and Stoffer 2017, Pohle et al. 2017), they continue to be largely overlooked for fossil lineages. Being able to detect and quantify multivariate relationships among traits within and among fossil lineages would enable novel connections between biological theory and data and provide a more robust foundation for documenting patterns of directional change in evolutionary history.

STATE SPACE MODELING TO UNLOCK NEW TESTS OF DIRECTIONALITY IN FOSSIL LINEAGES

PI: BECKETT STERNER

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MUTATION RATES, VARIATIONAL SPECIFICITY, AND LONG-TERM DIRECTIONALITY IN GENOME EVOLUTION

PI: ADI LIVNAT

While it is known that mutation rates vary across genomic sites, standard theory attributes no fundamental significance to this variation (Merlin 2016). Additionally, investigators have only been able to measure mutation rates as averages of various kinds (e.g., across the genome (Rahbari et al. 2016) or instances of a motif (Carlson et al. 2018)), limiting us to a low-resolution picture of mutation-rate variation. We have developed a method that enables studying the origination rates of target mutations in target base-positions, thus allowing us to test the possibility of long-term directionality in the origination of mutation. As a first target for this method, we have chosen the human hemoglobin S (HbS) mutation, which provides protection against malaria while causing sickle-cell anemia in homozygotes (Pauling et al. 1949, Allison 1954). We found evidence that this mutation originates de novo more frequently in sub-Saharan Africans – who have been experiencing intense malarial selection pressure for many generations – compared to northern Europeans, who have not, and in the beta-globin gene, where it provides protection against malaria, compared to the same mutation in the identical region in the delta-globin gene, which does not (Melamed et al. 2022). In other words, this mutation originates de novo more frequently in the gene and in the population where it is of adaptive significance (Melamed et al. 2022). This result challenges the notion of random mutation on a fundamental level (Melamed et al. 2022, Livnat and Melamed 2023). Our current project has two main goals: First, to simplify and standardize our methods in order to make them more easily and widely accessible to the scientific community, thus speeding up their adoption and the increase in the number of studies such as the HbS mutation one; and second, to continue examining empirically the possibility of long-term directionality in mutation origination in a variety of genes and organisms, as this may further motivate scientists to join in this effort to reevaluate the fundamental nature of mutation and its implications.

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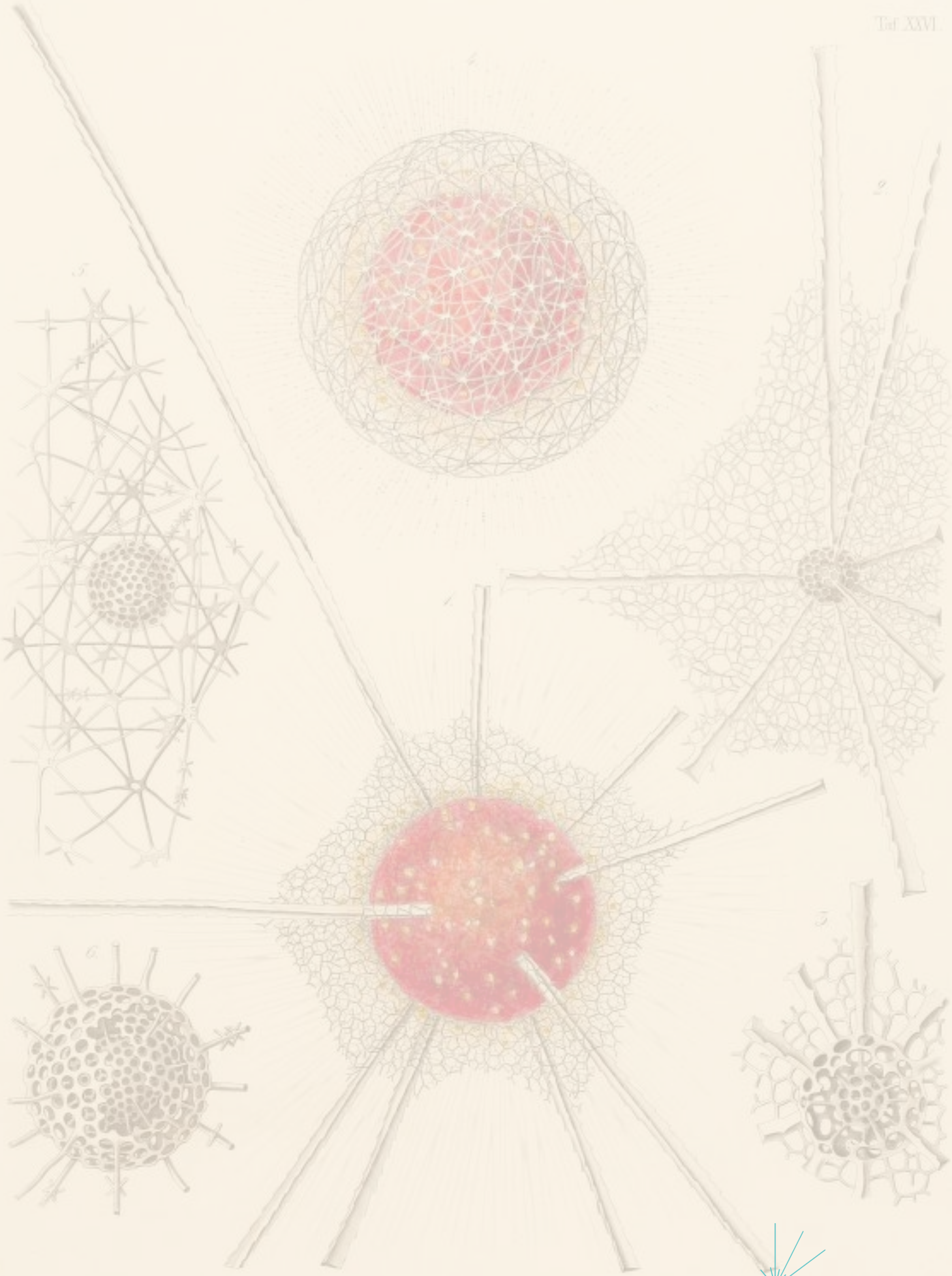

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