Schmidt Sciences

2026 Schmidt Science Polymath Award

Please complete the application questions below, save the file as a PDF, and upload it as part of your application in SurveyMonkey Apply. Your responses do not need to fit perfectly into the boxes below. Approximate word counts ("<N words") are provided as a guide for each question. Citations are not counted toward the word limit. All questions in this document are required. Please limit the use of figures/schematics and only include them if they will significantly enhance your application reviewer's understanding. You may include up to two simple figures throughout the whole document.

Name: **Ruben Perez-Carrasco**

1. What have you done in your main line(s) of research? Please explain using scientific detail with citations, in a way that non-specialists can understand. *(<500 words*)

How do cells tell time? There is no clock inside the cell, no universal pacemaker. Instead, timing emerges from the collective action of molecules, and cellular population. The speed of these processes determines when neurons differentiate, how tissues grow, and how embryos develop. Yet most mathematical approaches used to understand biological processes focus on static outcomes, such as steady states or final patterns. My research addresses this gap by asking how time itself emerges from physicochemical rules across scales from molecules to populations.

At the molecular scale, a central puzzle is how molecular machines adjust their pace. The bacterial flagellar motor, for example, must rotate faster or slower depending on external loads. How can a nanoscale machine tune itself? By modelling its stochastic dynamics, we showed that cells achieve this by adding or removing torque-generating stator units, keeping the motor in an optimal regime. Together with experimental collaborators we confirmed it is mechanically regulated for timing and efficiency [1,2], showing how modular molecular machines combine mechanical and biochemical scales to meet operational demands.

A similar molecular timing question is how time emerges in gene regulatory networks. Using dynamical systems theory, we uncovered the biophysical timing limits of how transcription-factor interactions encode precise switching timers, or oscillations with set frequencies [3,4,5]. To ground these predictions, I collaborated with synthetic biologists to build circuits that produced spatiotemporal patterns guided by Bayesian inference, linking mechanisms to data [6]. We further showed that small network motifs can support multiple timing behaviours regulated under external control [7,8], including circuits tuned near critical points that encode day-long slow-downs from minute-scale molecular lifetimes [9].

Timing is also central in development. Why do human embryos form neurons at half the speed of mice, despite a conserved genetic programme? In neurogenesis, we showed that network architecture buffers noise to produce spatiotemporal patterns using Minimum Action Path theory [10, 4]. Comparative expression data with mechanistic models revealed that protein stability largely explains species differences [11]. We later formalised this into a mathematical theory framing developmental timing as a physical symmetry—a conserved property of the gene-expression orbit—drawing on orbital equivalence [12]. This framework suggests ways to modulate tempo, for example in vitro neuronal differentiation, with implications for regenerative medicine.

These questions are not only kept at a molecular level, but also at tissue level, where collective behaviour generates new temporal rules. How do cell–cell mechanics integrates in the pace of development? Using vertex computational models constrained by neuroepithelial live-imaging showed that adhesion and contractility must be integrated with cell-cycle and differentiation dynamics to achieve correct patterning [13]. We later showed that standard computational models neglect these effects, producing artefacts in inference [14,15]. A similar principle appears in preimplantation embryos, where we showed that active cell competition remove less fit cells, ensuring robust embryogenesis and setting developmental tempo [16].

Across these scales, my work develops and applies mathematical and computational tools that allows us to understand how living systems measure, tune, and compute time from molecular machines to whole tissues.

[1] PNAS **114**:49 12952-12957 (2017)
[2] Sci. Adv. **8**:eabl8112 (2022)
[3] ACS Synth. Biol. **5**:6 459-470 (2016)
[4] Phys. Rev. Lett. **120**, 128102 (2018)
[5] J. R. Soc. Interface. **15**:20180157 (2018)
[6] Mol Syst Biol **16**: e9361 (2020)
[7] Cell Systems **6**:4, 521-530 (2018)
[8] iScience **26**:6 106836 (2023)
[9] Phys. Rev. E **111** 024213 (2025)
[10] Development **148**(14):dev197566 (2021)
[11] Science **369**:6510 aba7667 (2020)
[12] Development **151**(12):dev202950 (2024)
[13]Development 146 (23): dev176297 (2019)
[14] Phil. Trans. R. Soc. B37920230051
[15] Biophysica 2024, 4(4), 586-603
[16] Development (2024) 151 (2): dev202503.

Polymaths are expected to be intensely creative leaders who demonstrate an immense capacity for innovative new thinking or shifts in research directions that can lead to impactful breakthroughs given flexible resources. Successful candidates will have made significant

progress on multiple research problems while also showing a capacity for generating a continuing flow of innovative new ideas and approaches in a variety of areas.

2. What makes you a good fit for this program? *(<250 words)*

My research is driven by curiosity rather than by the predefined boundaries of physics, mathematics, or biology. This has given me a track record of tackling questions that no single discipline could address in isolation. Sometimes this has meant using mathematical tools to solve biological problems, such as identifying mechanisms that explain differences in developmental speed across species [11,12]. At other times, it has meant letting biology inspire new mathematical problems, such as my work on synergistic slowing down near critical points [9], rooted in gene regulation but with applications beyond biology. The same ethos runs through my research group, which brings together people trained in different sciences but united by curiosity, and extends to collaborations with experimentalists, theoreticians, and computer scientists.

This interdisciplinary outlook has also shaped my career path. Having worked in departments of physics, mathematics, and life sciences, I have learned to understand the languages, problems, and perspectives of each discipline. This has allowed me to recognise gaps in current knowledge and motivated me to build the communities needed to address them. I founded the London Mathematical Biology Conference (running since 2023) and co-organised the Royal Society meeting Interdisciplinary Approaches to Dynamics in Biology. These projects reflect my belief that only by bringing communities together can we generate new tools to address questions that remain out of reach otherwise.

These experiences have shown me that leaving one's comfort zone is not a risk but an opportunity to generate new understanding. It is also why I see myself aligned with the Polymath Award's ambition to support researchers who push into unfamiliar domains.

3. What about your work is most innovative, creative, adventurous, boundary-crossing? What do you consider to be the key ingredient that makes you a successful researcher? *(<500 words)*

Innovation in my work has come less from the questions themselves—which can sometimes be classical, such as how gene networks switch states or oscillate—and more from how I choose to attack them. My creativity lies in not changing the level of abstraction, reframing problems, and deliberately crossing disciplinary boundaries to generate tools that none of the fields could have developed in isolation.

One example is my use of orbital equivalence to study embryonic tempo. Developmental biologists already knew that mouse and human share similar genetic programs. Mathematicians already had tools to compare trajectories in dynamical systems. The creative step was to recognise that these could be combined. The result was not just the identification of protein degradation as the mechanisms behind neuronal differentiation tempo, nor just building a new mathematical framework with applications to other disciplines. It also provided a systematic quantitative definition of what it means for two species to follow the "same program" or to operate at the "different tempo", transforming descriptive biological observations into quantitative descriptions that refine the scientific question and allow to generate hypotheses and guide experimental design.

Another defining feature of my approach to boundary-crossing advance is the integration of data and modelling from the outset. Traditional mechanistic models in biology are elegant but often detached from data; data-driven approaches, by contrast, tend to strip away mechanism. I aim to bridge this divide by constructing models embedded from the beginning in a Bayesian inference framework [6–9], with biophysical priors and outputs that quantify uncertainty and guide experiments. The result is a new class of tractable models: neither simplified toys nor black boxes, but hybrid structures that both explain and predict. This approach is increasingly shaping how collaborators plan experiments and frame their questions.

One of the most exciting aspects of my work is uncovering unexpected links across fields once a common language is applied: embryonic cell competition can be cast in the framework of Lotka–Volterra predator–prey models from ecology; synthetic biology circuits become experimental testbeds for principles of gene regulatory logic shaped by evolution; and the operation of molecular motors can be dissected by the mathematics of stochastic differential calculus. Taking the risk to explore unfamiliar grounds has consistently opened new opportunities for discovery that would have remained invisible within a single discipline.

Overall I see science as a connected whole, where tools, concepts, and data move freely across domains. The novelty lies not in borrowing methods but in combining perspectives across physics, mathematics, and biology to answer questions none could have produced in isolation, providing insights with impact across the broad scientific community.

4. Describe a pivotal moment in your career by telling us about a time you sought out a challenge beyond your core discipline(s). How did you address it? *(<500 words)*

A turning point in my career came when I realised that the gene regulatory networks I was modelling in the context of embryonic neural tube patterning could also be probed in synthetic biology. The appeal was clear: synthetic circuits provide precise control and observables often inaccessible in embryos. But entering synthetic biology was not straightforward. The culture, language, and priorities of the synthetic biology community differed markedly from those in developmental biology, and the framing of meaningful questions required adaptation.

Rather than remaining on the modelling side, I chose to run some of the experiments myself in a collaborator's lab. This was not about becoming an experimentalist, but about critically examining how data are generated and what assumptions underpin them. I quickly saw how common modelling conventions—steady-state approximations, simplified heuristic modelling of gene regulation, neglect of growth-phase effects—misaligned with practice. Working through these details revealed where theory was over-idealised or blinded by variability, clarifying how to adapt models to experimental realities and design experiments that directly test predictions.

Although none of these experiments produced standalone publications, this period proved transformative. It gave me the vocabulary to communicate with synthetic biology collaborators, the insight to design models aligned with measurement constraints, and the ability to frame questions relevant across communities. It seeded projects that produced new theoretical and experimental results: engineering spatiotemporal stripes in synthetic bacterial strains, identifying novel circuit behaviours such as the mushroom bifurcation (resettable memory, transient detection), and characterising the AC/DC circuit (tunable oscillation synchrony and excitatory dynamics).

Finally, insights on the role of intrinsic noise in cell-state transitions were transferred back into developmental biology, revealing how evolution has shaped the cis-regulatory elements of the neural tube [cite Exelby], underscoring how boundary-crossing generates new knowledge not accessible in isolation. This experience reinforced my view of science not as parallel tracks of fenced disciplines, but as an integrated landscape where dismantling boundaries is essential for discovery.

Proposed Future Research Directions

The Schmidt Science Polymaths Program supports polymath researchers to expand their portfolios by exploring new lines of research that are substantively different from their ongoing and proven research activities. The program will award $500K USD per year for up to five years to support part of a research group. These grants are intended for the exploration of new ideas that use new technologies and insights that are generally too new or risky to garner regular support. In responding to the following prompts, please consider the current state of the subject(s) or problem(s) you intend to pursue and discuss the anticipated impact of your approaches.

5. If you were to receive the Polymath Award, what would you be most interested in researching? Briefly tell us about 1-3 intriguing subjects or problems you might work on, keeping in mind that the Polymath Award intends to support researchers venturing far beyond their established lines of research. Your proposed work and/or approach should be significantly different from your past work and innovative within the proposed field(s) or discipline(s). *(<500 words)*

Another field of biology in which timing is central is immunology. How long must receptor-ligand complexes persist before signalling is triggered? When does a T-cell irreversibly commit to activation, exhaustion, or memory? These questions are inherently temporal, yet most models in immunology remain static: focusing on affinity constants, endpoint measurements after therapy, or categorical cell state enumeration. My aim is to bring timing into the centre of immunology by linking molecular and cellular mechanisms across scales using dynamical systems, stochastic processes, and Bayesian inference, tools I have previously developed in developmental and synthetic biology.

Temporal complexity starts at the nanoscale: not in single receptor–ligand bond lifetimes, but in receptor-ligand cluster spatiotemporal dynamics, beyond classical kinetic proofreading models. T-cell, NK, and cytokine receptors operate in crowded membranes where complexes rapidly rearrange, form, and break. Yet most models collapse this richness into simplified affinity constants or on-off kinetics, overlooking spatiotemporal heterogeneities. I will use stochastic process theory and statistical mechanics (such as Lattice Boltzmann methods) to capture how receptor clusters assemble and set dynamic probabilistic thresholds over time. This reframing could explain why small shifts in binding kinetics yield large functional differences—a discrepancy repeatedly observed but lacking mechanistic account. With single-molecule and high-resolution microscopy, the opportunity is ripe to connect receptor-level dynamics with measurable outcomes.

Receptor dynamics drive cellular decision: but how do immune cells commit to activation, or exhaustion? Current approaches catalogue states using static assays (scRNA-seq, ATAC-seq), but they do not capture the timing or reversibility of transitions. New temporal tools—e.g. RNA velocity or live-cell reporters—now provide access to these dynamics, but theory has yet to exploit them. In developmental biology, we have shown how cell fates emerge through dynamical systems principles such as multistability, excitability, and critical slowing, which define windows of reversibility and points of no-return. I will transfer this framework into immunology: embedding single-cell time series into dynamical systems models analysed through bifurcation theory to reveal when transitions occur, their stability, and which signals precede irreversible commitment. This shift reframes immune regulation into a predictive theory of transitions, with direct implications for identifying when interventions such as checkpoint inhibitors are most effective.

Ultimately, immune decisions are made at the level of cell populations, unfolding across diverse timescales and shaped by heterogeneity. How do thousands of distinct clones, each noisy and variable, coordinate within tissues to generate a coherent response? Unlike developmental systems, where cells converge toward common fates, immune populations are heterogeneous. With advances in live imaging, we can now track the motility and interactions of immune cells during pathogen encounters. I propose to integrate these datasets with agent-based and multiscale models, using Bayesian hierarchical inference to link single-cell motility and activation to emergent population-level outcomes. This will reveal how stochastic single-cell behaviours aggregate into collective dynamics, and how population-level organisation emerges from mechanistic rules.

Across these scales, I will explore immunology not only as ‘who talks to whom,’ but as noise-driven dynamics across scales that shape systemic decisions. By embedding dynamical models directly in data anchored in biophysical hypotheses, I aim to provide new conceptual foundations for understanding, predicting, and ultimately controlling immune dynamics.

6. Why are you choosing to move in this direction? What makes you excited about this new direction? What is the potential impact of this research? *If you have described multiple subjects or problems in the previous question, you may choose to answer these questions for one, several, or all of your proposed new directions. (<250 words)*

I am excited by immunology because it poses a dynamical systems problem of unparalleled richness: millisecond-scale receptor binding, hour-scale fate decisions, and week-to-year clonal dynamics all coexist in the same system. Stochasticity here is not a nuisance but a fundamental ingredient, shaping immune activation, persistence, and memory formation. The challenge—and the opportunity—is to reveal how timing and noise across these scales connect into principles, transforming what are often scattered, qualitative observations into a quantitative set of rules that predict immune decision-making.

From a mathematical and computational perspective, this richness creates problems I am eager to tackle. For example, inferring cell–cell interaction rules from live imaging requires new hierarchical Bayesian frameworks that can extract biophysical parameters directly from movies. Meeting this challenge will mean going beyond current inference methods by coupling AI-based image analysis with deep-learning Bayesian approaches such as Sequential Neural Posterior Estimation into a full inference pipeline. This pipeline will translate live-imaging recordings into posterior distributions over biophysical parameters (e.g. motility persistence or synapse formation probability), embedding uncertainty directly in the output. Crucially, these posteriors will not only link observations to mechanism but also guide experimental design by identifying the most informative experimental conditions to refine our understanding (e.g. recording durations, frame frequency, or cell density).

Thus, this work will not only advance immunology by generating quantitative predictive tools that will impact immune interventions, particularly those where timing and scheduling are critical, such as immunotherapy regimens. The tools developed here would be directly applicable to questions like when to administer checkpoint inhibitors, how to optimise CAR-T cell expansion and persistence, and how to modulate vaccine responses through dose timing. At the same time they will advance mathematical and computational methods with broad impact across biology.

7. How would you approach moving into this new direction? What makes you uniquely positioned to pursue this direction? What challenges do you foresee? *(<250 words)*

To move into immunology, close collaboration with experimentalists is essential. I have recently joined a Life Sciences department with a strong immunology community spanning molecular to population scales. For example, Prof. Dan Davis investigates receptor organisation at the immune synapse using super-resolution microscopy to visualise nanoscale clustering of signaling molecules and immune synapse dynamics in live cells. Dr. Nadia Guerra generates NK cells with fluorescently tagged receptors (e.g. NKG2D-GFP, Ly49A-RFP) to track interacting NK-tumour populations. Finally Prof. Cristina Lo Celso applies live imaging to study immune–stromal interactions in the haematopoietic niche, revealing how immune cells behave in 3D living tissues. These collaborations are not aspirational: we have already begun project discussions including analysis of existing datasets. These collaborations will enable me not only to have a ground understanding of the field, but also to propose and conduct new assays to challenge theoretical predictions.

I am uniquely positioned for this transition because I have a track record of working across theory and experiment. I have not only collaborated with experimental biologists of different fields but also spent time at the bench myself understanding how data are generated, to grasp perspective essential to design models. I will extend this approach by recruiting interdisciplinary postdocs who can work jointly with my group and experimental labs. This model is already proving effective: two of my current PhD students combine experiments with modelling, one studying metabolism in neurogenesis and another engineering synthetic gene circuits with intracellular spatial interactions.

The main challenge is bridging disciplinary language and priorities in a new field I am not expert in, but this is precisely the space where I thrive. By embedding mathematical models directly into experimental design and co-developing assays with collaborators, I aim to ensure the theory is not abstract but becomes a working part of the immunology toolkit.

8. How would pursuing these subjects constitute a significant shift when compared to your current and past work? What would this award allow you to do that you otherwise wouldn't be able to? *(<250 words)*

This project represents a major shift from my current work because I am new to the field of immunology. While the underlying questions of dynamical systems and stochasticity are shared, the immunological context, experimental systems, and language are entirely different. Entering this complex field in a meaningful way requires time and sustained momentum—something that smaller, narrowly focused grants cannot provide.

The intellectual challenge is also new. Immunology involves multiscale stochasticity of a kind rarely present in development: receptor fluctuations at the nanoscale, cell fate transitions, and clonal dynamics in tissues all interacting simultaneously. Addressing this requires the development of new theoretical tools, in particular AI-powered multiscale Bayesian frameworks. Building such methods is a substantial effort that goes well beyond what can be supported by a standard project grant.

Finally, the scale of the problem calls for a larger team. A single postdoc or student could only scratch the surface of one scale, whereas a coordinated group could simultaneously probe receptor, cellular, and population levels. This award would provide the resources to assemble such a team, ensuring that the project is not fragmented but truly integrative. All in all, the Schmidt Sciences Polymath Award would give me the freedom to take the necessary risks to explore immunology through dynamical systems lens, placing timing and noise-driven variability at the core of a quantitative language to interrogate immune activation, fate, and coordination across scales.