EUROPEAN SCIENCE FOUNDATION
SETTING SCIENCE AGENDAS FOR EUROPE

EUROCORES Programme
European Collaborative Research

Synthetic Biology: Engineering Complex Biological Systems (EuroSYNBIO)

Call for Outline Proposals

What is EUROCORES?

The ESF European Collaborative Research (EUROCORES) Programmes offer a flexible framework for researchers from Europe to work on questions which are best addressed in larger scale collaborative research programmes. The EUROCORES Programmes allow excellent researchers from different participating countries to collaborate in research projects 'at the bench'. They also allow, when appropriate, colleagues from non-European countries, for example the US, to participate. The Programmes encourage and foresee networking and collaboration of researchers to achieve synthesis of scientific results across the programme, to link to related programmes, and to disseminate results.
EUROCORES Programmes allow national research funding organisations in Europe and beyond to support top class research in and across all scientific areas, by matching the needs articulated by the scientific community with their strategic priorities.
Funding decisions on the projects and the research funding remain with the national research funding organisations, based on international peer review operated by ESF. ESF also provides support for networking the researchers and for the scientific synthesis of research results and their dissemination[(1)]. This way, the EUROCORES Scheme complements the EC Framework Programme and other collaborative funding schemes at European level.

For further information see:
http://www.esf.org/eurocores

[(1)] Until December 2008 this is supported through a contract with the European Commission under the Sixth Framework Programme (EC Contract no. ERAS-CT-2003-980409). From January 2009 onwards this support will be provided by the national Funding Organisations participating in the Programmes.

Synthetic Biology: Engineering Complex Biological Systems (EuroSYNBIO)

Following agreement with funding organisations in *Austria, Belgium, Czech Republic, Finland, Germany, Italy, Luxembourg, The Netherlands, Norway, Romania, Slovakia, Slovenia, Switzerland, United Kingdom,* the European Science Foundation is launching a Call for Outline Proposals for Collaborative Research Projects (CRPs) to be undertaken within the EUROCORES Programme EuroSYNBIO. EuroSYNBIO will run for 4 years and it includes national research funding, as well as support for networking and dissemination activities provided through the ESF[1].The Programme aims to support high quality multidisciplinary research.

Outline Proposals are to be submitted by 6th March 2009, 12h00 noon CET. It is expected that Full Proposals will be invited by 21st April 2009 with 16th June 2009 as expected deadline for submission.

A Programme-specific website can be consulted for the latest updates at **http://www.esf.org/eurosynbio**

Background and objectives

Synthetic biology is the rational (re-)design of biological systems with useful properties. It is a highly interdisciplinary endeavour (Figure 1) and can be viewed from two angles: First, the engineering perspective, which entertains the hope of transforming biotechnology into a true engineering discipline with the corresponding reliabilities and accuracies in design.

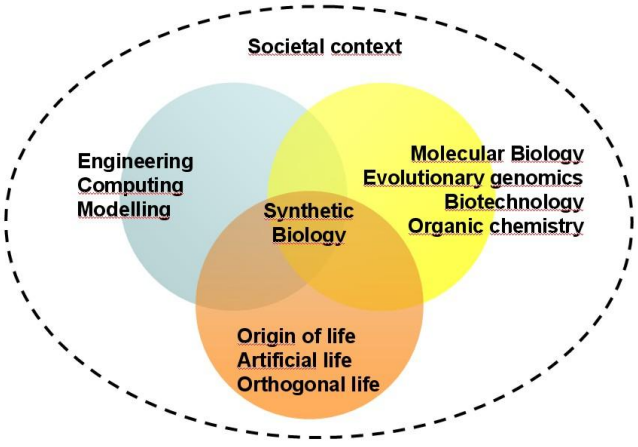

Figure 1. The highly interdisciplinary field of synthetic biology

Second, the synthetic focus provides a unique tool for confirming or challenging our current understanding of molecular events and system function, because only if we can reliably rebuild cellular properties can we claim intellectual mastership ("What I cannot build, I cannot understand", R. Feynman).
Both these aspects of synthetic biology, transforming bioengineering and advancing understanding through synthesis, need to undergo a fundamental transition to be able to tackle systems-level questions. This transformation will happen on two fronts: First, there is the need to transform existing and develop novel computational tools that allow taking our current computational procedures from the analysis of single items to the systems level. Second, it is necessary to support the computational change-of-scope with the same change in our workflows towards the "biosystems design laboratory".
The final element in this transition is the societal context, as synthetic biology needs to be aware of and effectively manage its societal impact. Therefore, the societal context will be integrated in its various forms from an early stage of the scientific and engineering endeavour, bearing in mind that it might be a vital element in successfully guiding the future development of synthetic biology.

The first achievements in synthetic biology include the design and implementation of synthetic genetic circuits, the design of novel biochemical pathways for the production of valuable pharmaceuticals, and the *de novo* synthesis of bacterial genomes. The ultimate ambition of the field is to extend the mastery of biological engineering to systems complex enough to deal with grand challenges such as the design, synthesis and delivery of novel therapeutic treatments, affordable and precise diagnosis of diseases, novel routes to vaccines, production of liquid transportation fuels, bioremediation of pollutants, biocompatible carbon sequestration, and efficient manufacturing of biopharmaceuticals and biochemicals.

Scientific goals

This EUROCORES Programme aims to address core strategic challenges of synthetic biology, thereby providing a solid scientific and technological basis for the development of this strongly transformative field. These challenges include:
[i] the rational assembly of systems in a context of Darwinian evolution,
[ii] the development of computational design tools for biosystems design,
[iii] the biosystems design laboratory, and
[iv] the potential societal and ethical impact of successfully overcoming these challenges.

Research topics

To address the objectives outlined above, EuroSYNBIO invites research proposals that deal with – but are not limited to - the following topics:

1) System assembly and molecular and cellular complexity in a context of Darwinian evolution
The concept of truly rationally assembling parts to systems requires the ability to either fully anticipate the effect that the implementation of a novel component into a system will produce – which will be difficult to achieve in a system so complex as entire cells - or the capacity to drastically limit this effect by design (orthogonality). Essentially, there is the need to develop autonomous functional modules or subsystems that reduce the design complexity to manageable levels and then to connect such subsystems in a reliable fashion. This endeavour will have to face and eventually overcome two major hurdles: **[i]** the evolutionary background and Darwinian selective pressure that any biological system is subject to as a perpetual working condition and **[ii]** the inherent ability of biological components to establish interactions with their molecular surroundings.

a) Autonomous parts:
Research aimed at the conceptualisation and development of comprehensively characterised minimal biological parts and minimal biological functions of key importance for the design process. The issue at hand is how to start with existing biological molecular assemblies or networks, which appear naturally as highly context-dependent elements, and end up with reasonably orthogonal parts or modules that operate stably over a long period of time. This might involve research ranging from implementing orthogonal molecular interfaces to fine-tuning of dynamic properties, and could be applied to a variety of existing and novel model systems relevant for functional systems design.

b) Subsystems:
Research directed **[i]** at the assembly of subsystems based on autonomous parts to identify crucial elements that have to be considered in the design process, and **[ii]** at the implementation of novel subsystem functionalities.

c) Synthetic systems:
Research on all aspects relevant to rational system assembly, in particular research involving:
[i] the implementation of suitable standardised interfaces between subsystems;

[ii] the implementation of orthogonality in cellular systems;

[iii] and the assembly of synthetic systems with substantially novel properties following a synthetic biology approach.

d) Refactoring genomic chassis:
Research on suitable host systems to receive designs of increasing complexity. This can involve the design of reduced or even minimal genomes or the design of alternative minimal systems working on an orthogonal basis. This effort also includes novel ways **[i]** to decrease and limit the effects of Darwinian evolution on the designed systems and **[ii]** to facilitate chromosomal replacement and ectopic gene implantation.

e) Understanding and overcoming the physico-chemical constraints imposed by cell architecture on the performance of synthetic circuits:
Designed circuits do not operate in a vacuum, but instead in the specific milieu of a living cell, made up from a highly specialised 3D scaffold with a spatial division of work and functions. There is thus the need to understand the rules by which the blueprint of the cell structure imprinted in the genome are then projected into a given 3D operative unit.

2) Computational design tools
The consistent application of the engineering design paradigm to biological systems is the hallmark of synthetic biology. The rational assembly of parts to devices and systems and anticipating and counteracting the impact of their implementation into existing chassis cannot be done without a solid and versatile modelling framework. There is an acute need for an extensive computational infrastructure and new computational methods that specifically support the rational design goals and the abstraction/orthogonality/assembly approach of synthetic biology. This is in contrast, for example, to the currently existing ad hoc systems-oriented computational methods developed to treat and analyse data.
The synthetic biology effort should develop in an open-source, user-friendly computational environment that will facilitate collaborative editing, implementation and iterative revision of synthetic biology endeavours (part design, circuit building, synthetic genomes, etc.). To address these needs, research in the following topics is invited:

a) Computational interchange standards, ontologies and collaborative environment:
Synthetic biology will generate a large number of components and modularised functional devices and systems that need to be catalogued and characterised. Moreover, these have to be made interoperable and embedded in contexts that enable their use as building blocks in system design. This strongly requires ontologies and appropriated computational resources, model repositories and design frameworks that are currently not available and that should hence be developed.

b) Data mining & integration:
Research and tool development are needed for automatic extraction of design-specific information from literature and existing biological, chemical and physical databases, and its efficient integration in a standardised, interoperable way into the design workflows.

c) Parts design:
This includes tools for the elaboration of stand-alone biological parts that complement relevant experimental, directed evolution driven approaches to provide suites of parts with different design parameters and novel functions.

d) Model-based systems design, analysis and optimisation:
Research is invited on the elements of a comprehensive biological design framework that integrates design tools from the part or minimal function level to the design of complex systems. This could involve:

[i] developing a set of standard modelling objects to describe basic functions of standardised biological parts,

[ii] establishing mechanisms for instantiating modelling objects according to the users' selections of parts from the registry,

[iii] developing interfaces between registries and repositories and modelling / simulation tools through standardised protocols, and

[iv] providing novel methods for computer-assisted circuit design, including optimisation of circuit layout according to behavioural specifications provided by the user, and specifications of allowable parts characteristics such as binding affinities of transcription factors that are consistent with behavioural specifications.

3) The biosystems design laboratory
Generally, while our analytical capabilities in molecular biology have advanced to the systems level ("systems biology"), our synthetic capabilities have not yet taken this leap. Such a leap would entail three crucial elements:

a) Megabase-scale DNA synthesis:
The re-writing of substantial sections of, or even entire, genomes requires access to non template-driven methods of DNA synthesis. However, while in principle feasible, these methods are currently highly error-prone and limited by the assembly of oligonucleotides to rather small DNA segments. Therefore, research is invited that either addresses the current limitations in *de*

novo DNA synthesis or explores novel technologies in megabase-scale DNA synthesis.

b) The role of analysis:
Designing dynamic synthetic systems relies on the availability of parameters that allow predicting the system behaviour. These parameters are usually unavailable, because they are difficult to acquire. Furthermore, systems are mostly described in terms of fundamental physico-chemical parameters such as binding constants, rather than by parameters that might have more impact in a design context, such as the rate of promoter clearance. Therefore, research in this section could be directed at enabling the facile and rapid acquisition of design-relevant data in suitable throughput.

c) Automated system assembly:
The sheer scale of system-level synthetic approaches such as minimising or re-synthesising genomes to the implementation of system-wide engineering protocols makes it highly impractical to proceed with the current standard laboratory practices. Therefore, research directed at expanding the existing synthetic capabilities in biological system design is invited, for example by miniaturisation, parallelisation and automation of current laboratory protocols or the implementation of completely novel, system-scalable methods.

4) The social context
Synthetic biology touches upon fundamental philosophical ("a minimal genome" – a minimal version of life?), safety (are complex synthetic systems safe?), and security (can such systems be abused?) questions, many of them inherited from a societal context that has been formed by earlier debates on genetic engineering. In addition, the transition from a discovery science to an engineering discipline may require significant changes in the way intellectual ownership is handled. Therefore, the Programme will foster close interactions with social scientists and other relevant stakeholders including policy makers, industry, civil society, the media and the general public. Answers to the above questions will guide the further development of the synthetic biology community in a fashion that is compatible with the requirements and mores of society. In this respect, the EuroSYNBIO Programme is to address:

a) Philosophical and ethical implications:
These include, but are not limited to, the very definition of life, which will influence the way living systems are understood, just as the unpredictable behaviour of systems with emergent properties and the concepts of orthogonal life might create new ethical issues related to the field.

b) Safety and security:
What has to be done to make complex synthetic systems inherently safe to prevent unintended consequences? How can synthetic biology contribute to solve current biosafety challenges (e.g. prevention of unintentional transfer of genetic material) and make biotechnology even safer and more reliable? Furthermore, developments in synthetic biology are to be framed within the global concern on misuse of new technologies.

c) Governance and regulation:
Are there aspects in synthetic biology that justify new regulatory approaches or are the existing regulatory frameworks sufficient? How will synthetic biology be influenced by the concept of "governance" and the potential inclusion of multiple stakeholders in guiding its development.

d) Intellectual property rights:
How does the transition from a discovery science to an engineering science based on the exchange and re-utilisation of standardised parts and systems, frequently only marginally improved, impact intellectual ownership in the biotechnology sector?

e) Effective public dialogue:
How can the communication between science and stakeholders, in particular the public, be made more effective and engaging? How can the scientific biology community ensure that the eventually resulting public debate on synthetic biology is based on a rather accurate reciprocal perception of challenges, risks, and potentials?

Programme deliverables

The Programme aims at delivering *inter alia*:

• Identification of fundamental physico-chemical constraints that limit the performance of engineered circuits implanted in a cell and delineation of the rules of 3D design imprinted in the cell genome.

• One robust conceptual frame to demarcate minimal, orthogonal biological functions and their translation into specific DNA sequences – or molecular devices - that can be efficiently used in the construction of a regulatory architecture and the implementation of synthetic functionalities.

• A robust conceptual framework to implement standards that define the interfaces between orthogonal subsystems.

• Concepts for the development of biological chassis that are resistant to Darwinian evolution – either by enhancing artificially the fidelity of the gene replication/expression machinery or by

resorting to alternative information-bearing molecules.
• The construction of chassis of various complexities from bacteria to lower eukaryotes to mammalian cells that have been designed for specific engineering purposes such as metabolic engineering in strains of reduced genomic complexity, and drug discovery in mammalian cells with synthetic gene networks.

• A suite of powerful computational resources that support the design of biological systems from *de novo* DNA synthesis to genome revision control to complex systems dynamics.

• Miniaturised chip-architectures for highly parallel system analysis, engineering, and system assembly.

• A scientifically well-founded and society-grounded framework that addresses the synthetic biology-specific societal aspects of biosafety, biosecurity, ethics, intellectual ownership, governance and public dialogue.

• A conceptual framework to treat the ownership of the constituents of synthetic systems in a thoroughly transformed bioengineering landscape of part registries, re-utilised part, and shared development.

Programme synergies

Fostering synergies and interlinking the elements:

The EuroSYNBIO Programme addresses the challenge of implementing the synthetic biology approach to systems engineering across a broad set of disciplines, from cellular biology via technology development to ethics and law. It is foreseen that, whilst the majority of the Collaborative Research Projects (CRPs) will be driven by the natural sciences and engineering, the social sciences will be key contributors. In this regard, it is anticipated that the questions of societal and economic impacts of synthetic biology be addressed in two ways: 1) whenever appropriate, embedded into a project that has otherwise an engineering or natural science focus, or 2) in the form of projects dedicated to investigating one or several specific topic(s) within the social context of synthetic biology. Such dedicated projects have a cross-Programme mission and should develop a clear strategy on how to engage the projects focussing on natural sciences and engineering, just as these have to show a clear strategy on how to communicate and articulate with the projects dedicated to societal impacts.

The Review Panel may request the inclusion of relevant societal questions to the project before the full proposal stage.

To ensure that the various scientific initiatives progress optimally and in an articulated fashion, the Programme will hold annual meetings. They will discuss the research progress of all projects, emerging issues or developments affecting several or all projects or the community at large, explicitly including societal aspects. Selected external speakers may be involved to address specific topics of collective interest.

Guidelines for applications

(Outline and Full Proposals)

Collaborative Research Project (CRP) proposals from individual scientists or research groups eligible for funding by the organisations participating in the Programme will be accepted for consideration in the EUROCORES Programme EuroSYNBIO.
Scientists or groups not applying for or not eligible to apply for funding from these organisations (including applicants from industry), can be associated with a proposal where their added scientific value is demonstrated. Their participation as Associate Partners in a project must be fully self-supporting and will not be financially supported by the participating funding organisations.

Proposals are only eligible, if they fulfil the following **criteria**:

- Proposals must involve, as a minimum, three eligible Principle Investigators (PIs) from **three different countries.**
- A maximum of 50 % of the Individual Projects (IPs) in a Collaborative Research Project (CRP) can come from one country.
- Proposals must involve more PIs than Associated Partners

Applications should normally be for three years although applications for shorter or longer time periods may be considered depending on the rules of the participating funding organisations. Taking into account the selection and approval processes, the successful projects are expected to begin their activities in **January 2010**.

Online submission of applications

Outline and Full Proposals will be submitted online. Applicants should follow the proposal structure as indicated in the application template for outline proposals available on the Programme website at: **http://www.esf.org/eurosynbio**.

On this Programme website, links to information on national funding eligibility and requirements as well as to a EUROCORES Glossary and Frequently Asked Questions (FAQs) are available.

Prior to submitting Outline Proposals, all applicants have to contact their national funding organisations in order to verify eligibility and to ensure compliance with their relevant organisations' granting rules and regulations (see contact persons listed on page 10).
At the time of online submission of the Outline Proposals, the Project Leader is asked to confirm this on behalf of all the participants in the CRP.

Outline Proposals

Outline Proposals are invited by 6th of March 2009 12h00 noon CET.
Outline Proposals will be examined by the participating funding organisations for formal eligibility. Therefore, it is crucial that all applicants contact their national funding organisation prior to submitting their proposals.
In compliance with the rules and regulations of the participating national funding organisations, the requested funds under the EUROCORES Programme EuroSYNBIO can include salaries for scientific and technical staff, equipment as well as travel costs and consumables within the project, specifying the amount requested from each Funding Organisation. National policies may also require the proposal to contain specific additional information. Applicants should be aware that the participating funding organisations can make significant adjustments to the requested funds in order to bring these in line with their rules and regulations.

Applications will be assessed according to a set of criteria in a two-stage procedure, to ensure a thorough selection of scientifically excellent proposals. At the outline stage, the Review Panel will select proposals with potential for scientific excellence, by applying the following criteria:

- Relevance to the Call for Proposals
- Novelty and originality
- European added value (scientific)
- Qualification of the applicants

An Outline Proposal submitted must comprise:

- A short description of the CRP (max. 1200 words, including objectives, milestones, methodologies (for example experiments and fieldwork);
    - Short description of how (and why) the partners contributing to the CRP will work together;

- Short CVs of Project Leader (PL), all PIs and Associate Partners (max. one page each, including five most relevant publications);
- Estimated budget (consistent with the rules of relevant national funding organisation) tabulated according to a provided template.

Associated Partners (APs) are also considered part of a CRP and will be assessed as such at both the Outline and Full Proposal stage.

It is important that ethical clearance of relevant national or international committees has been obtained before funding is granted. It is the responsibility of applicants to clarify this with their national contact points.

It will be assumed that arrangements for the handling of IPR (Intellectual Property Rights) will be in place within projects, following the applicable national legislation and national funding organisation's rules. Applicants are strongly urged to have such arrangements in place, covering all research groups (including any associated groups) before the start of the projects. It is expected that the results obtained by the projects supported under this EUROCORES Programme will be placed in the public domain.

Full Proposals

Full Proposals will be invited following the recommendations of the Review Panel. The deadline for full proposals will be announced later, but is expected to be around 16th June 2009.

Please note that only applicants who submitted an Outline Proposal can submit a Full Proposal.

For the Full Collaborative Research Project (CRP) proposals, the most important selection criterion is "Scientific quality". Other criteria include interdisciplinarity (according to the scope of the call), qualification of applicants, level of integration and collaboration, feasibility and appropriateness of methodologies, European added value, relation to other projects (risk of double-funding) and suitability of budget requirements.

The Full Proposals will be assessed by at least three independent external expert referees who are selected by the ESF from a pool of scientists suggested by the participating funding organisations, the Review Panel and the ESF office. A list of all referee names used for the international peer review will be published once the selection process has been completed.

After receiving the referee reports, they will be made available (anonymous) to the applicants for their information and for commenting (optional). The Review Panel will rank all Full Proposals based on the assessment of the Full Proposal, the anonymous referee reports and the applicant's responses to these.
The Review Panel will create a ranked list consisting of the best Full Proposals and will subsequently make recommendations to the Management Committee for the funding of these proposals. The actual granting of the funds to the Individual Projects on the ranked list will depend on the total amount of funds available in each participating Funding Organisations. The use of funds in a project will be subject to the rules and regulations of each participating Funding Organisation as well as to the national laws of those countries.

Full proposals must include a well-argued scientific case (both for the collaboration envisaged and for the individual contributions), a list of participants, a detailed tabulated budget and other supporting information. A single, common scientific case must be made throughout the proposal to demonstrate an aim for scientific synergy and integration of multinational expertise. In addition, the amount requested from each national funding organisation has to be clearly and separately specified. Detailed instructions on requirements and how to complete the application will be made available once Full Proposals are being invited.

The **Project Leader** will be the main CRP proposal contact point for ESF for the duration of the project. He/she will be responsible for representing the Collaborative Research Project, for its participation in programme activities, and for any reporting requirements placed on the project as a whole.

All **Principal Investigators** will be responsible for dealing with the requirements concerning the contributions of their own funding organisation.

Programme Structure and Management

Programme Structure

The overall responsibility for the governance of the programme lies with a *Management Committee*, whose membership is formed by one representative from each participating funding organisation (usually a senior science manager) together with an ESF representative.

Proposal assessment and selection are the responsibility of an international, independent *Review Panel*. The members of this panel are leading scientists, appointed by ESF following suggestions from participating Funding Organisations. The membership of the Review Panel will be available on the Programme website for information. The Review Panel is also expected to monitor the overall scientific progress of the programme.

The Scientific Committee which is formed by the Project Leaders of all funded CRPs will be responsible for proposing a Programme work-plan including networking activities for scientific synergy in the EUROCORES Programme. They will also advice and support the EUROCORES Programme Coordinator in the coordination of networking activities.

Programme Networking

Networking activities are designed to strengthen the science objectives of this EUROCORES Programme by promoting coherence in the activities of the science community involved. This will provide the European added-value which is the central objective of any EUROCORES Programme.

Networking and collaboration within EUROCORES Programmes takes place at two levels:

1. between the various Individual Projects within each Collaborative Research Project (CRP) and
2. between the funded CRPs within the programme as a whole.

The intra-CRP activities are supported through the research grants each participant receives from the participating funding organisations in the given CRP. The cross-CRP activities are funded through contributions to the EUROCORES Programme.

The intra-CRP collaboration is motivated by the nature of the CRP's research objectives, i.e., by the scope and the complexity of the questions it deals with. In a CRP, the participating groups have the opportunity to gather the required critical mass to successfully address the objectives and challenges of their project.

The cross-CRP networking and collaboration is stirred by the aims and the nature of the EUROCORES Programme. The theme which was the basis of this EUROCORES Programme has been selected for its clear need of collaboration in the proposed field. The funded CRPs will collectively set up and further streamline this new collaboration. To this end, the CRPs will engage the programme participants and, when of clear benefit, colleagues from outside the programme in joint activities such as:

- Programme-wide meetings or conferences
- Working Group meetings for the exchange of information and results across the CRPs;
- Joint scientific meetings or summer schools;
- Short term visits;
- Development and delivery of joint training schemes;
- Seminars, Workshops, symposia, invited sessions either stand-alone or as part of other larger events;
- Common web-facilities and publications.

Through active participation of scientists in the above mentioned activities, not only existing collaborations are enhanced but new and strategic partnership opportunities are also identified.
Furthermore, these activities may provide opportunities to explore aspects of the programme which are not covered by the funded research projects.

The integrative activities between the CRPs will help to strengthen the field by building coherence within the emerging research community and will serve as a platform for the research work which is conducted in the programme.

Project members are expected to participate annually in at least one cross-CRP activity.

When submitting your proposal, please note that the costs for networking within your CRP should be budgeted for in your proposal. Funds for networking between the CRPs will be centrally managed by the ESF through contributions from the participating funding organisations.

Programme evaluation

A “light” Mid-Term evaluation, involving the Review Panel, will evaluate the overall progress of the Programme. Here, the Review Panel may comment on the CRPs’ work plan in relation to the objectives of the overall Programme. A final evaluation at the end of the Programme will evaluate the achievements of the whole EUROCORES Programme.

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