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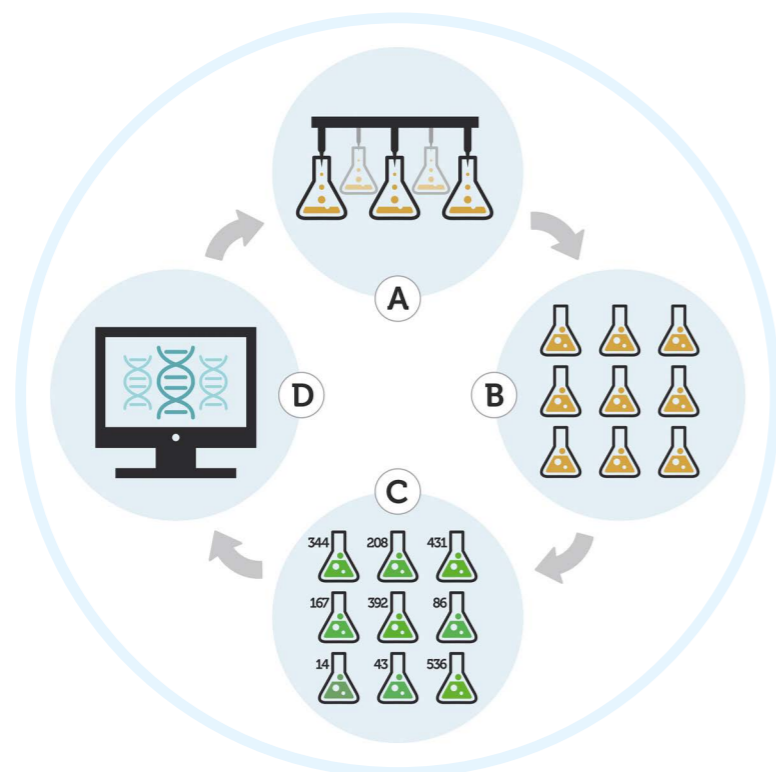
# GENE GAME™

CLOSED-LOOP COMBINATORICS & AI-DRIVEN  
BIOPROCESSING

# EMPOWER YOUR THROUGHPUT WITH **GENE GAME™**

Combinatorial screening and optimisation are crucial for many disciplines of life sciences, bioengineering, and biotechnologies. The “one-at-a-time” method and statistical approaches such as the response surface methodology based on factor design experiments are usually used. Such an optimisation takes a long time and is labour-consuming as it relates to performing hundreds of experiments in which various formulations are tested. Furthermore, the “one-at-a-time” method assumes that there are no interactions among optimised factors. In most cases, this hypothesis is not true and gives only suboptimal results. To reduce the number of experiments despite many variables and their optimised levels, stochastic search strategies have been developed.

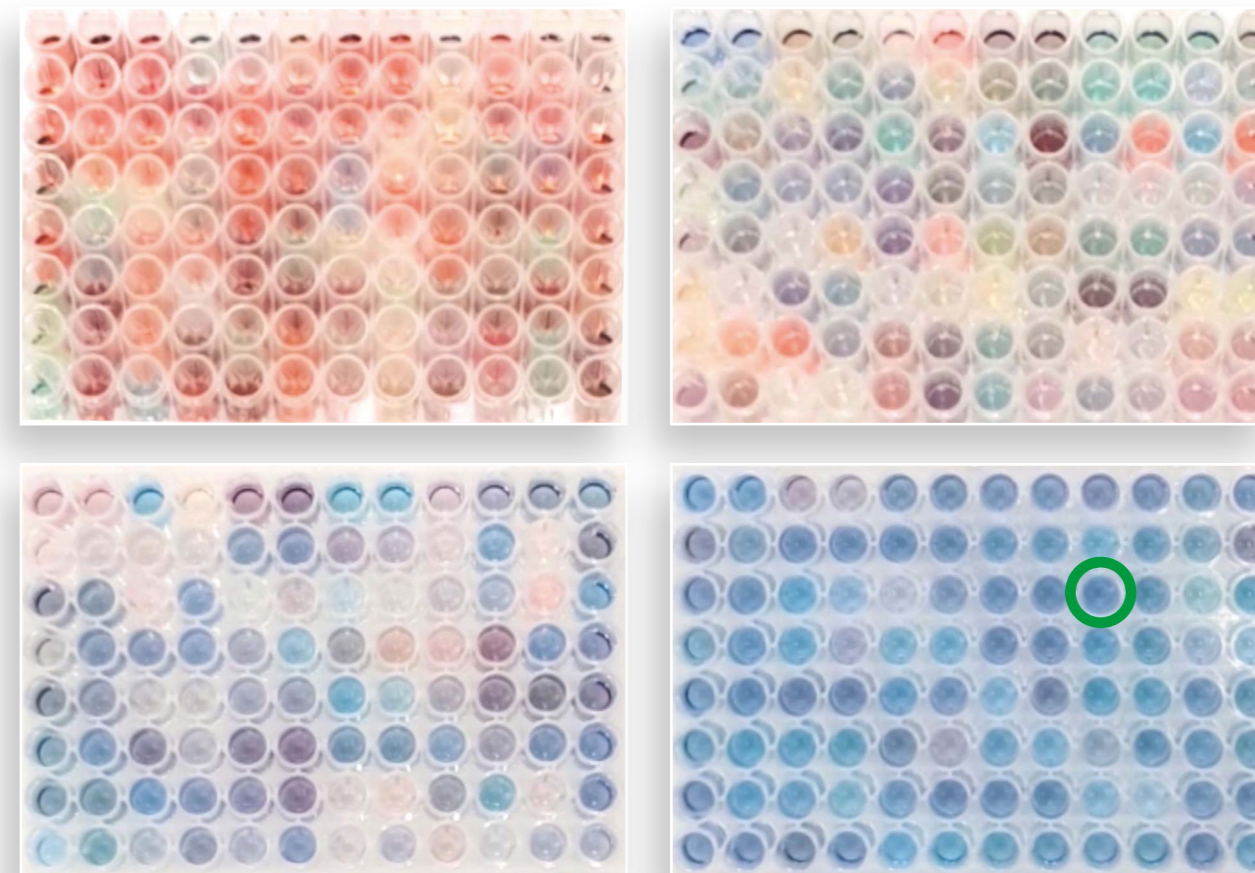
**Gene Game™** is the Intelligent Screening System for evolutionary solving multidimensional biological, biomedical, and biochemical problems. Through integration with the most popular HTS schedulers and lab high-capacity instrumentation, **Gene Game™** automates sample preparation, experiment processing and results reasoning in a closed-loop manner. It means that the results collected during a single set of high throughput experiments do not require analysis, and next set of experiments can be planned and performed automatically without human involvement, based on mathematic calculations. This iterative circular process is much more effective than the human subjective mind and manual experimentation on limited numbers of samples (Pic. 1).



**Picture 1. Diagram of the evolutionary optimisation of bioprocess with Gene Game™ in a closed-loop manner.** The high-throughput screening operator defines the optimisation problem in fitness formula and determines the list of optimised parameters and their levels (concentrations). Due to integration of **Gene Game™** with a robotic arm, liquid handlers, plate readers, and other instruments, the optimisation is conducted continuously without human involvement between cycles (generations). Each cycle contains the same steps: (A) making formulations in accordance with the generated dispensing list; (B) incubation of various formulations; (C) signal readouts for fitness evaluation; (D) genetic algorithms processing *in silico* and generation of a new dispensing list for the next cycle. The efficiency of optimisation depends on a quality of the biochemical assay and a number of samples and cycles.

Artificial intelligence core of **Gene Game™** is based on genetic algorithms that generate high-quality solutions in the optimisation and search problems by relying on the bio-inspired process of natural selection. The algorithms repeatedly modify a population of individual probes. At each set of experiments, based on the obtained results, the genetic

algorithms select the most promising probes and rearrange their formulas by crossing together and by introducing random changes. Over successive experiments, the population of probes “evolves” toward an optimal solution defined by the operator (e.g., biomass production, luminescence enhancement, lymphocytes activation etc.) (Pic. 2).



**Picture 2. Proof of Work. Evolutionary optimisation of the RGB dyes to maximise blueness using Gene Game™.** Each dye was optimised at 151 levels, giving the search space equal to 3,442,951 (3 components optimised within the 0-30  $\mu$ L range and 0.2  $\mu$ L resolution). The known global maximum was the mixture containing only blue dye (R=0.0  $\mu$ L, G=0.0  $\mu$ L, B=30.0  $\mu$ L). This solution (marked with a green circle) was found in the 4<sup>th</sup> generation of 96 RGB combinations with a total of 384 samples, without replicates. RGB formulations on in the first generations were prepared randomly, the next ones were determined by genetic algorithms.

**Gene Game™** solves the major limitations of the existing high-throughput screening centres, concerning their linear mode of action, i.e., the results collected during a single set of experiments require human analysis and reasoning, before the next set of experiments can be performed. The main idea of **Gene Game™** is going towards the concepts

introduced by futurologists of the 20<sup>th</sup> century of Intelligent Laboratory Automation (ILA), Total Laboratory Automation (TLA), or Automatic Drug Factory (ADF). This innovative software implements our vision of futuristic laboratory without humans, in which robots conduct high-throughput experiments and make AI-driven discoveries.

**References.** Sadoch, J, Pyc, M, Urbanowicz, A, Iglewski, A, Pilarski, R. High-throughput evolutionary optimization of the induction medium towards recombinant protein production in BY-2 tobacco. *Biotechnology and Bioengineering*. 2021; 118: 676– 689. <https://doi.org/10.1002/bit.27594>

# GENE GAME™.

## THE ARTIFICIAL INTELLIGENCE SOLUTION

### DATA EXPLORATION IN MULTIDIMENSIONAL SEARCH SPACE

#### APPLICATIONS

- Combinatorial screening of chemical compounds repositories for their selectivity on the chosen metabolic pathways
- Chemosensitivity tests on patients' individual cancer cells for finding individualised cocktails of anti-cancer drugs for their personal anti-cancer therapies
- Modelling disease from omic data for its better diagnosis, prognosis, and treatment
- Optimisation of stem cell media towards their differentiation potency into various types of cells
- Finding buffers and chemical solutions for efficient crystallization of biological proteins and peptides
- Optimisation of bioprocesses and biotechnologies, e.g. production of therapeutic monoclonal antibodies or chemotherapeutic agents in bioreactors
- Finding optimal content of buffers and physical factors for optimal reactivity of recombinant enzymes
- Searching monoclonal antibody libraries for chosen antigens
- Modelling evolution processes for better understanding and verification of evolution theories, concepts, and hypotheses
- Determining tertiary and quaternary structures of macromolecules, such as proteins and nucleic acids

#### FEATURES

##### Interface

Cross-platform browser support (Windows, Linux, MacOS)

##### Algorithms

- Conducting up to 10 evolutionary processes up to 100 000 generations each
- Encoding of at least 100 parameters at 100 levels in a sequence of appropriate length
- Encoding of chromosomes in a binary system and using floating-point numbers
- Generation of a population with at least 10 000 000 individuals
- Defining genetic operations (two-point and multi-point crossover, mutation, and inversion)
- Adaptive function scaling (linear scaling, sigma truncation, and power law scaling)

- Various selection methods (roulette wheel selection, rank selection, threshold selection and crowding selection)
- Random selection of the initial population with an option to define genotypes manually

##### Functionality

- Visualisation of evolutionary process and exporting charts in PNG, JPEG, TIFF and PDF formats
- Generation of statistics for each generation with a preview of historical data
- Manual chromosome editing and adaptive value settings
- Saving of selected populations and generations of the evolutionary process
- Opening a population file and continuing the population evolution
- Mathematical formula editor for defining adaptive functions

##### Data import and export

- Importing individual adaptation data from readers and high content imagers (Biotek Cytation, BMG Pherastar, Perkin Elmer Envision, Perkin Elmer Opera Phenix, Molecular Devices ImageXpress)
- Importing individuals ID using a barcode reader (Agilent Barcode Reader, Generic Barcode Reader, RVSI VR4000)
- Exporting a solution recipe for every individual to a liquid handling station (Tecan Evo, Agilent Bravo, Hamilton Vantage/Star/Nimbus, Becman Coulter Biomek, Formulatrix Tempest, Perkin Elmer Janus, Labcyte Echo 500 series)
- Exporting identification data of individuals for a plate labeller (Agilent Microplate Labeller)