Supporting Information for

Fully Automated Molecular Design with Atomic Resolution for Desired Thermophysical Properties

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Table S1. A survey of work applying CAMD for chemical engineering problems*

Property estimations / MINLP solutions	Group Contribution **(GC)**	Quantitative Structure-Property Relationship **(QSPR)**	Quantum Mechanics based Method **(QM-based)**
Genetic Algorithm **(GA)**[1-6]	• polymer: materials for semiconductor encapsulation, 1993~1995[7-9] • small molecules: alternative refrigerant, 1995[8] • solvent: LL extraction, 2000[10] • solvent: LL extraction, 2007[11] • solvent: antioxidant solubilization, 2014[12] • solvent: relative energy difference and solubility parameters, 2014[12] • solvent: extractive reaction, 2016[13] • solvent: ab/desorption process, 2017[14] • IL: heat transfer, 2013[15] • IL: electrical conduction, 2013[15] • IL solvent: LL extraction, 2013[15] • IL solvent: Naphthalene solubilization, 2013[15]	• solvent: LL extraction, 1995[16] • small molecules (for drug design): lipophilicity, length, solvent accessible surface, dipole moment, 2000[17] • polymer (enzyme inhibitor): ΔG of RNA folding, RNA sequence length, 2002[18] • small molecules (for drug design): number of H-bond donors/accepters, docking geometry, 2005[19] • small molecules: enzyme-substrate binding energy, structure similarity, 2008[20]	• solvent: LL extraction, 2017[21] • polymer: dielectric constant, 2016[22] • solvent: reaction rate constant, 2017[23]

Simulated Annealing **(SA)**[24-29]	• small molecules: log(K_{ow}), 1996[30] • small molecules: alternative refrigerants, 1998[31] • solvent: LL extraction, 1998[31] • small molecules: alternative refrigerants, 1998[32] • solvent: LL extraction, 1998[32] • solvent: LL extraction, 2002[33, 34] **HSTA** • solvent: LL extraction, 2006[35]	• small molecules: molecular compactness, 1996[30]	
Genetic Algorithm & Simulated Annealing **(GA-SA)**[36]	• solvent: LL extraction, 2017[37]		• IL: LL extraction, 2017[38] • IL: LL extraction, 2017[39]
Ant Colony Optimization Algorithm **(ACO)**[40, 41]	• solvent: LL extraction, 2015[42] **EACO**		
Tabu Search **(TS)**[43]		• metal-ligand complex: electronegativity, density, toxicity and oxidation state, 2005[44] • IL: gas refrigerant separation, 2010[45]	
Solver Package	• polymer: mechanical strength, 1996[46] **GINO** • IL: azeotrope separation, 2012[47] **GAMS/CPLEX** • IL: gas refrigerant separation, 2010[45] **GAMS/CPLEX**	• metal-ligand complex: electronegativity, density, toxicity and oxidation state, 2005[44] **GAMS/DICOPT** • polymer: glass transition temperature, density and heat capacity, 1999[48] **GAMS/DICOPT++**	
Outer Approximation **(OA)**[49-51]	• solvent: extractive reaction, 2002[52] • solvent: LL extraction, 2002[52] • solvent: CO_2 absorption		

	process, 2016[50] • small molecules: alternative refrigerants, 1996[53]		
Interval-based Global Optimization Algorithm[54]	• polymer: mechanical strength, 1996[46]		
Branch-and-Reduce Algorithm[55]	• small molecules: alternative refrigerants, 2003[56] • solvent: LL extraction, 2013[57] • solvent: crystallization, 2013[57]		
Exhaustive Search with Reduced Combinatorial Complexity	• solvent: LL extraction, 1983[58] • solvent: LL extraction, 1986[59] • solvent: LL extraction, 1991[60] • solvent: gas adsorption, 1991[60] • solvent: extractive distillation, 1991[60] • solvent: extractive distillation process, 1994[61] • solvents: extraction, 1999[62] • solvent: extractive distillation, 1999[62] • solvents: extraction process, 1999[63] • solvent: crystallization, 2006[64] • IL: applications on heat transfer, 2013[15] • IL: electrical conduction, 2013[15] • IL solvent: LL extraction, 2013[15] • IL solvent: dissolution of Naphthalene, 2013[15] • polymer: density and glass transition temperature, 2015[65] • surfactant: UV sunscreen, 2015[65] • solvent: LL extraction, 2015[65]		

	• solvent: extraction, 1989[66] • small molecules: alternative refrigerant, 1989[66] • polymer: semiconductor encapsulation, 1989[66]		
*the format of the content is (materials: properties or problem, year)[reference]			

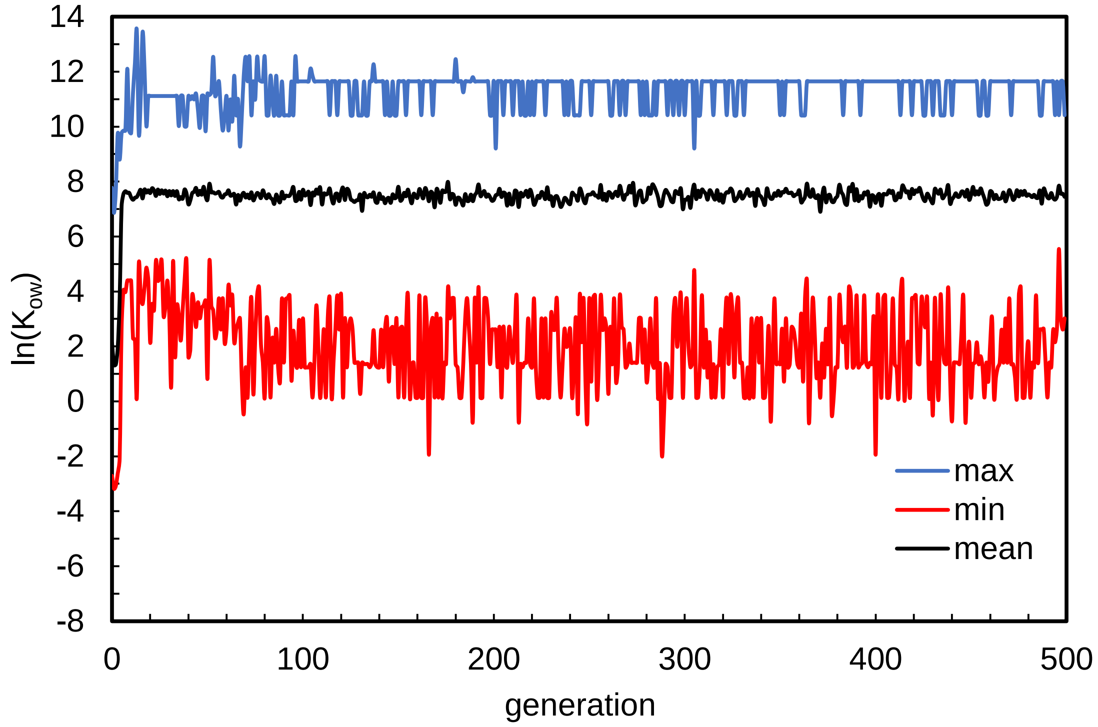
Table S2. Data structure of species generated from crossover (Figure 2) and mutation (Figure 3).

Name	propanal	acetone	propane	methylglyoxal	propanamide	1-butene	1-propanol
Index	1,2,3,4	1,2,3,4	1,2,3	1,2,3,4,5	1,2,3,4,5	1,2,3,4	1,2,3,4
Gene ID	1,1,2,7	1,2,7,1	1,1,1	1,2,7,2,7	1,1,2,7,8	2,2,1,1	1,1,1,6(or 7)
Parent index	0,1,2,3	0,1,2,2	0,1,2	0,1,2,2,4	0,1,2,3,3	0,1,2,3	0,1,2,3
Bond order	0,1,1,2	0,1,2,1	0,1,1	0,1,2,1,2	0,1,1,2,1	0,2,1,1	0,1,1,1

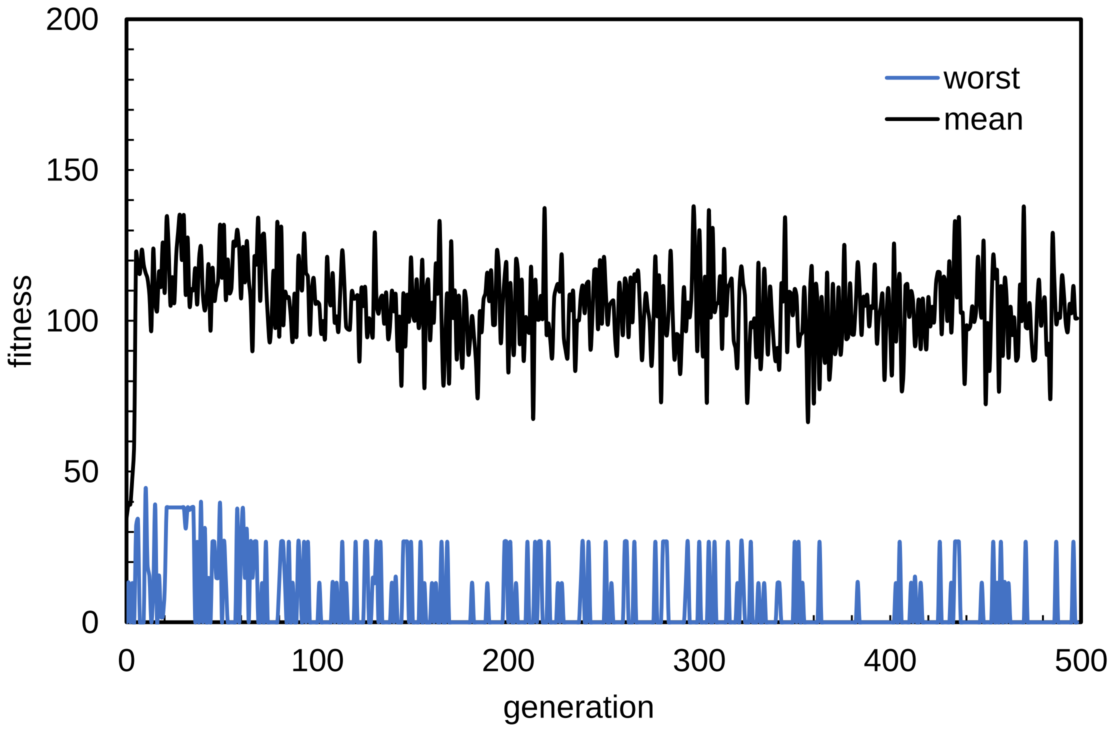
Table S3. The best species in the first 60 generations for the 3 case studies

	Case 1		Case 2		Case 3	
Generation	SMILES	$\ln(K_{ow})$	SMILES	$\ln(K_{ow})$	SMILES	$\ln(K_{ow})$
0	CN(C#C)C#C	4.389	COOONN	-1.082	NC(=C)C(=O)O	-0.8437
1	CCC=C(C)C	7.7733	C=NC(=C)C	3.8963	NCC(=CN)O	-1.4445
2	COOOC(=CC)C	6.8588	NC(=C)Cl	3.9112	NN=CC(OO)O	-2.513
3	CCC(=CC)C	7.6764	NC(=C)Cl	3.9112	NN=CC(OO)O	-2.513
4	COOOC=C(CC)C	8.0653	CN(C)C	4.2034	NN=CC(OO)O	-2.513
5	COOOC=C(CC)C	8.0653	OON(OCl)O	2.4706	NO	-2.8658
6	COOOC=C(CC)C	8.0653	NOON(NCl)Cl	4.0802	O=CCC(=O)N	-2.6287
7	COOOC=C(CC)C	8.0653	CCOON(C#CC)O	4.2995	NNC(C=N)O	-3.524
8	COOOC=C(CC)C	8.0653	CCC#CN(CC=N)O	3.3162	OOC(C=NCC(=O)O)O	-3.9144
9	COOOC=C(CC)C	8.0653	CON(Cl)C	4.0833	OOC(C=NCC(=O)O)O	-3.9144
10	COOOC=C(CC)C	8.0653	COCN(C#CC)O	3.5399	OOC(C=NCC(=O)O)O	-3.9144
11	COOOC=C(CC)C	8.0653	COCN(C#CC)O	3.5399	OOC(C=NCC(=O)O)O	-3.9144
12	COOOC=C(CC)C	8.0653	CNC(=CCl)N	3.1996	OOC(C=NCC(=O)O)O	-3.9144
13	COOOC=C(CC)C	8.0653	ON(Cl)Cl	4.3672	NNO	-4.0701
14	COOOC=C(CC)C	8.0653	COCN(O)C	2.4965	NNO	-4.0701
15	COOOC=C(CC)C	8.0653	CN(OCO)Cl	2.0233	NNO	-4.0701
16	COOOC=C(CC)C	8.0653	CN(OCO)Cl	2.0233	NNO	-4.0701
17	COOOC=C(CC)C	8.0653	CN(OCO)Cl	2.0233	NNO	-4.0701
18	COOOC=C(CC)C	8.0653	CN(OCO)Cl	2.0233	NNO	-4.0701
19	COOOC=C(CC)C	8.0653	CN(OCO)Cl	2.0233	NNO	-4.0701
20	COOOC=C(CC)C	8.0653	CN(OCO)Cl	2.0233	NNO	-4.0701
21	COOOC=C(CC)C	8.0653	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
22	COOOC=C(CC)C	8.0653	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
23	CCCC(=C)C	7.8536	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
24	CCCC(=C)C	7.8536	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
25	CCCC(=C)C	7.8536	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
26	CCCC(=C)C	7.8536	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
27	CCCC(=C)C	7.8536	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
28	CCCC(=C)C	7.8536	CN(OCO)Cl	2.0233	NNNC(=C(O)O)N	-4.0029
29	CCCC(=C)C	7.8536	CN(OCO)Cl	2.0233	NNNC(=C(O)O)N	-4.0029
30	CCCC(=C)C	7.8536	CN(OCO)Cl	2.0233	NNNC(=C(O)O)N	-4.0029
31	CCCC(=C)C	7.8536	CN(OCO)Cl	2.0233	NNNC(=C(O)O)N	-4.0029
32	CCCC(=C)C	7.8536	CN(OCO)Cl	2.0233	NNNC(=C(O)O)N	-4.0029
33	CCCC(=C)C	7.8536	CN(OCO)Cl	2.0233	NNNC(=C(O)O)N	-4.0029
34	CCCC(=C)C	7.8536	CN(OCO)Cl	2.0233	NNNC(=C(O)O)N	-4.0029
35	CCCC(=C)C	7.8536	CN(OCO)Cl	2.0233	NNNC(=C(O)O)N	-4.0029

36	CCCC(=C)C	7.8536	CN(OCO)Cl	2.0233	NNNC(=C(O)O)N	-4.0029
37	CCCCC	7.9779	CN(OCO)Cl	2.0233	NNNC(=C(O)O)N	-4.0029
38	CCCCC	7.9779	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
39	CCCCC	7.9779	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
40	CCCCC	7.9779	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
41	CCCCC	7.9779	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
42	CCCCC	7.9779	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
43	CCCCC	7.9779	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
44	CCCCC	7.9779	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
45	CCCCC	7.9779	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
46	CCCCC	7.9779	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
47	CCCCC	7.9779	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
48	CCCCC	7.9779	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
49	CCCCC	7.9779	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
50	CCCCC	7.9779	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
51	CCCCC	7.9779	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
52	CCCCC	7.9779	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
53	CCCCC	7.9779	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
54	CCCCC	7.9779	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
55	CCCCC	7.9779	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
56	CCCCC	7.9779	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
57	CCCCC	7.9779	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
58	CCCCC	7.9779	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
59	CCCCC	7.9779	CN(OCO)Cl	2.0233	NNNNNO	-3.9721
60	CCCCC	7.9779	CN(OCO)Cl	2.0233	NNNNNO	-3.9721

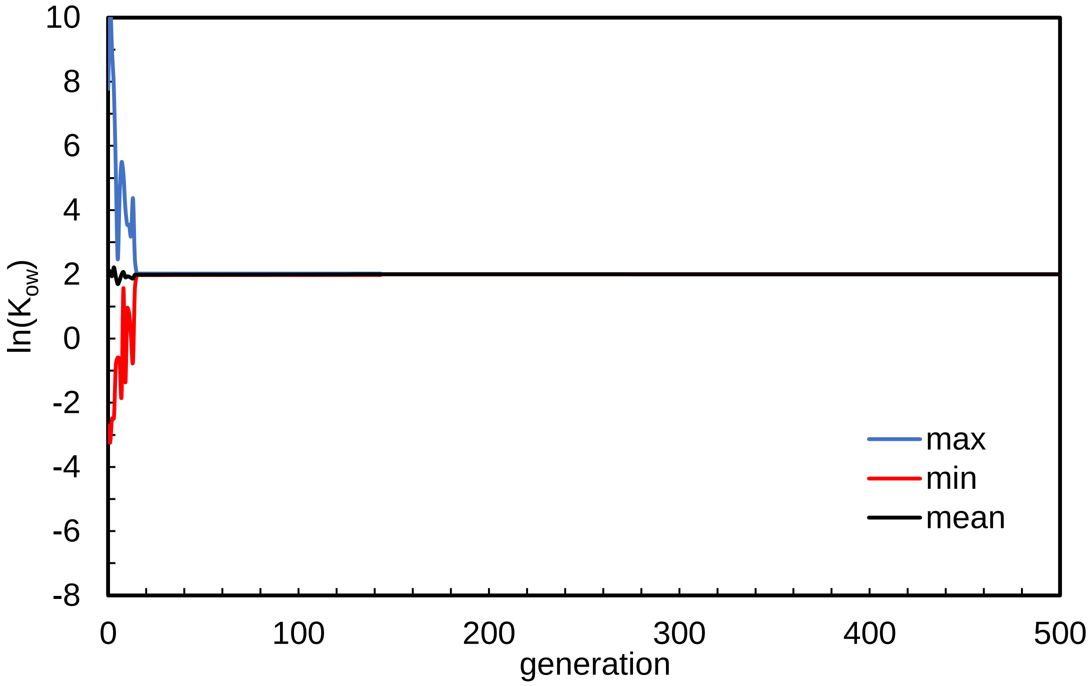

14
12
10
8
6
4
2
0
-2
-4
-6
-8
ln(Kow)
0
100
200
300
400
500
generation
max
min
mean

(a)

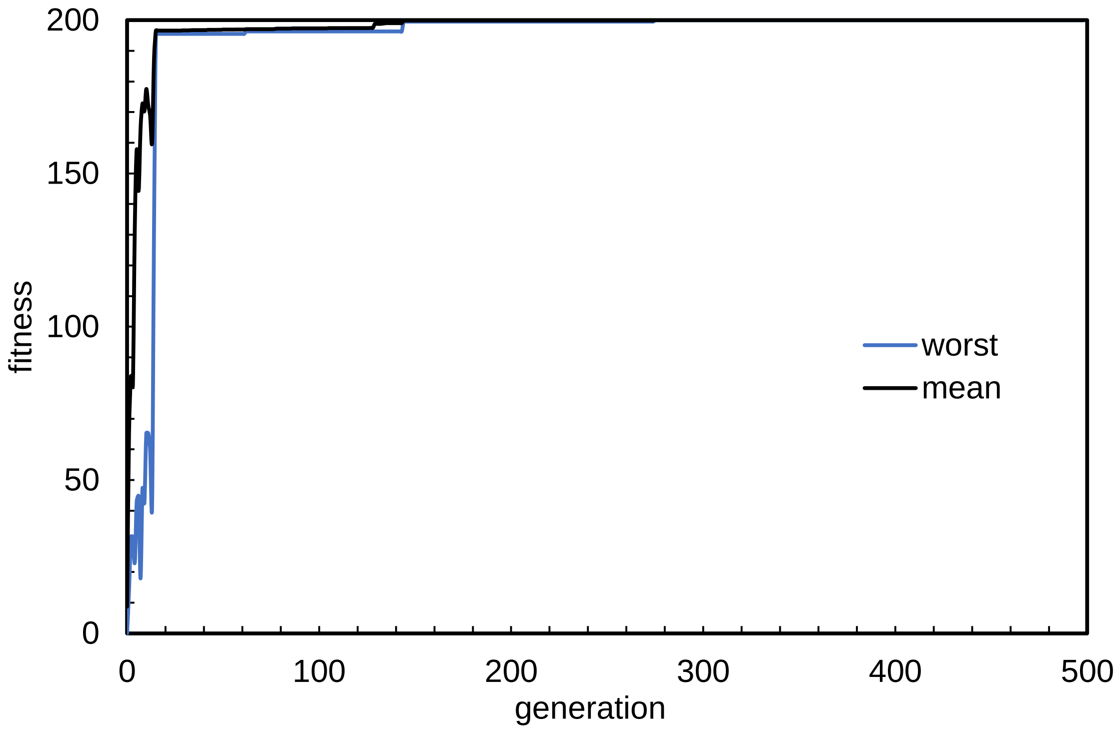

200
150
100
50
0
fitness
0
100
200
300
400
500
generation
worst
mean

(b)

Figure S1. The evolution of mean (mean), maximum (max), and minimum (min) values of $\ln K_{ow}$ (a) and the mean and worse fitness (b) with generation in case 1 study before SA.

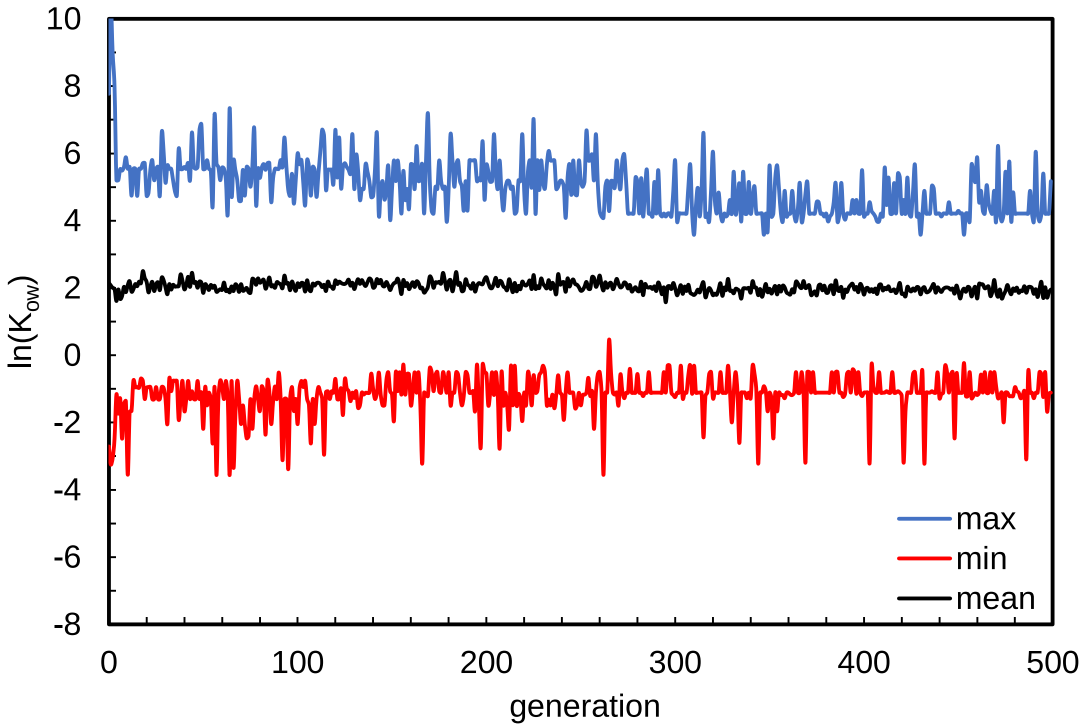


(a)

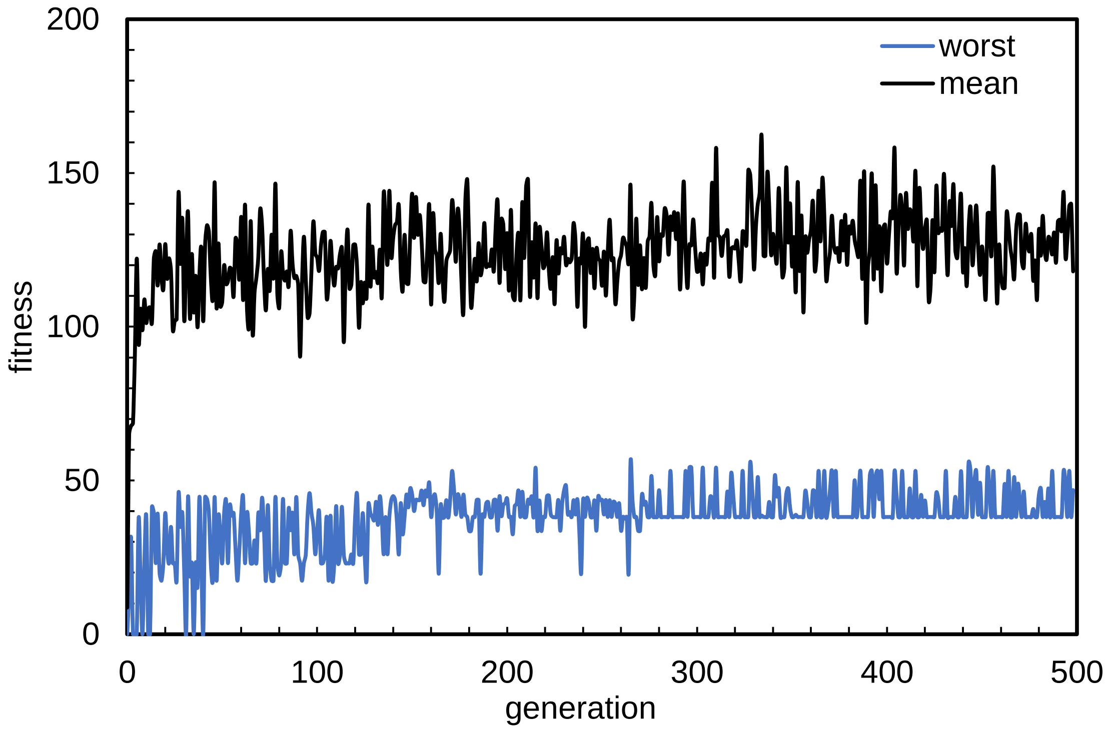


(b)

Figure S2. The evolution of mean (mean), maximum (max), and minimum (min) values of $\ln K_{ow}$ (a) and the mean and worse fitness (b) with generation in case 2 study.

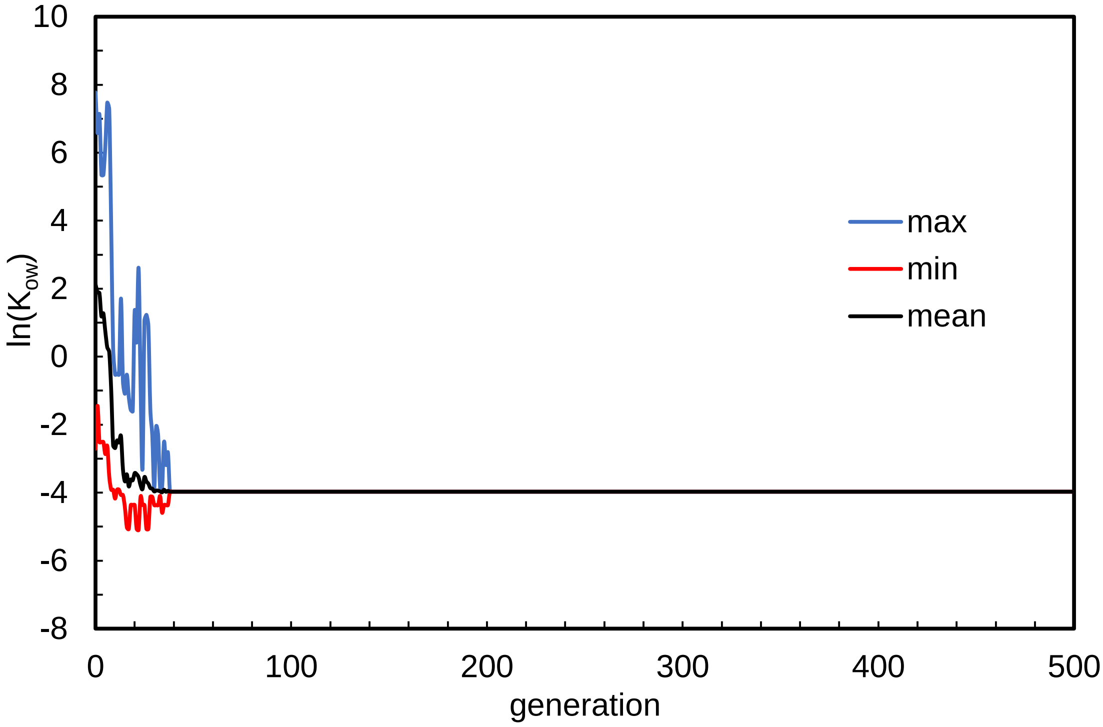


(a)

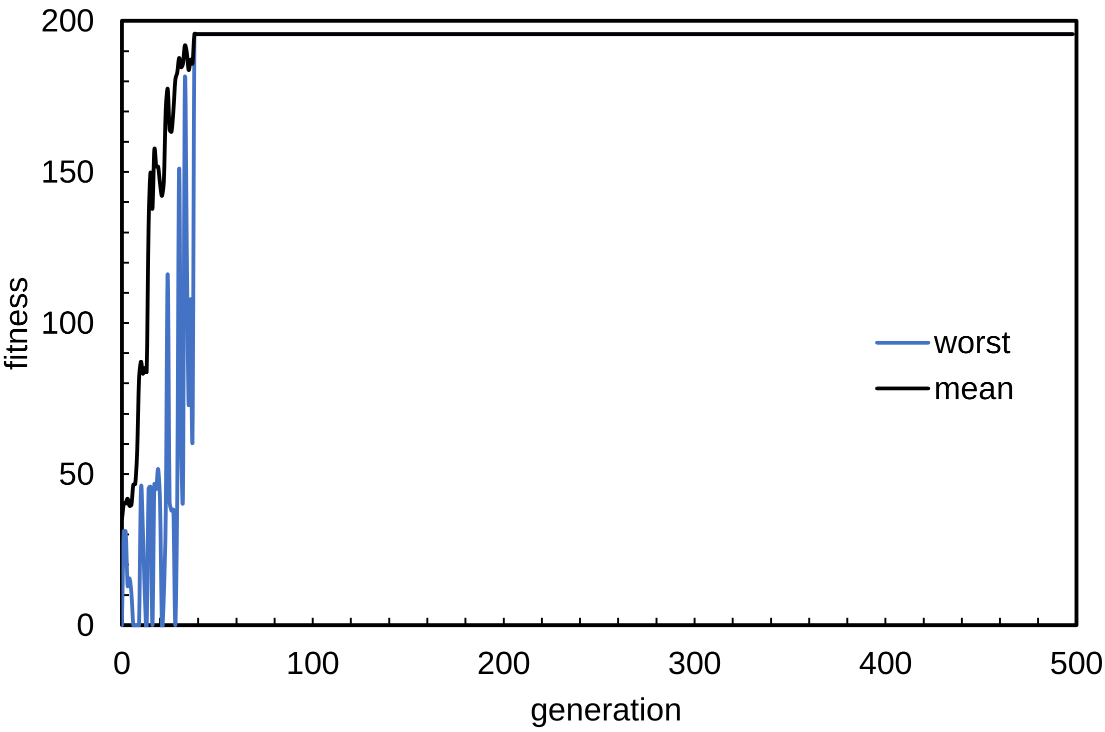


(b)

Figure S3. The evolution of mean (mean), maximum (max), and minimum (min) values of $\ln K_{ow}$ (a) and the mean and worse fitness (b) with generation in case 2 study before SA.

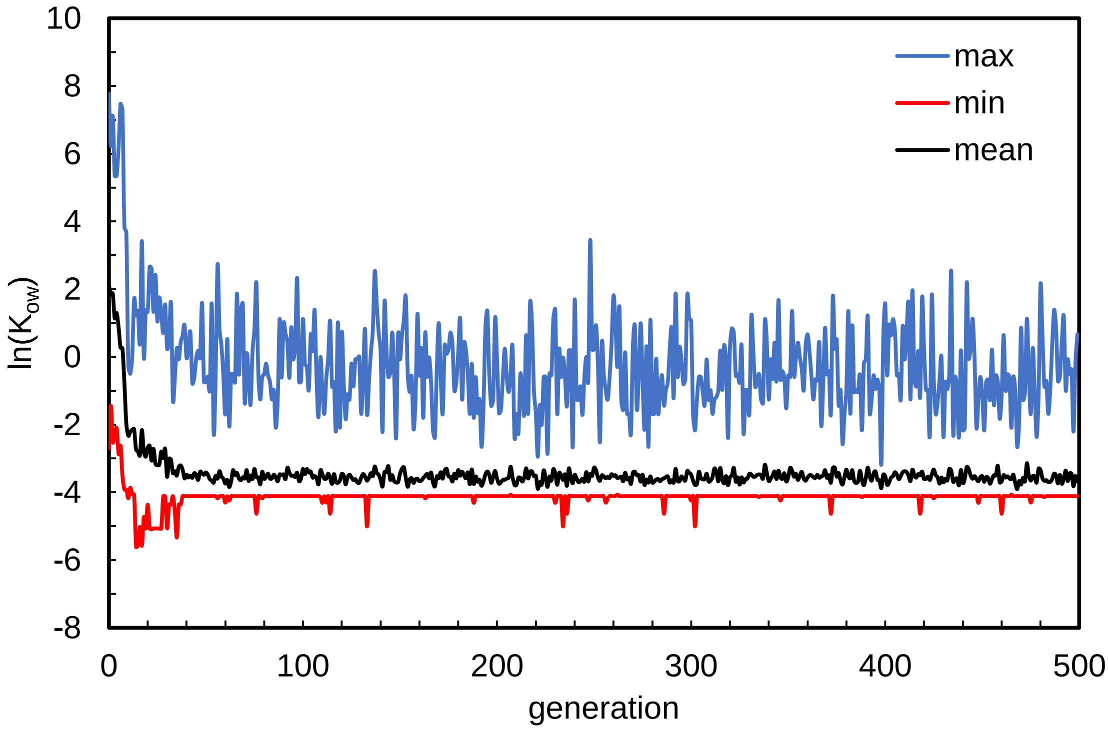


(a)

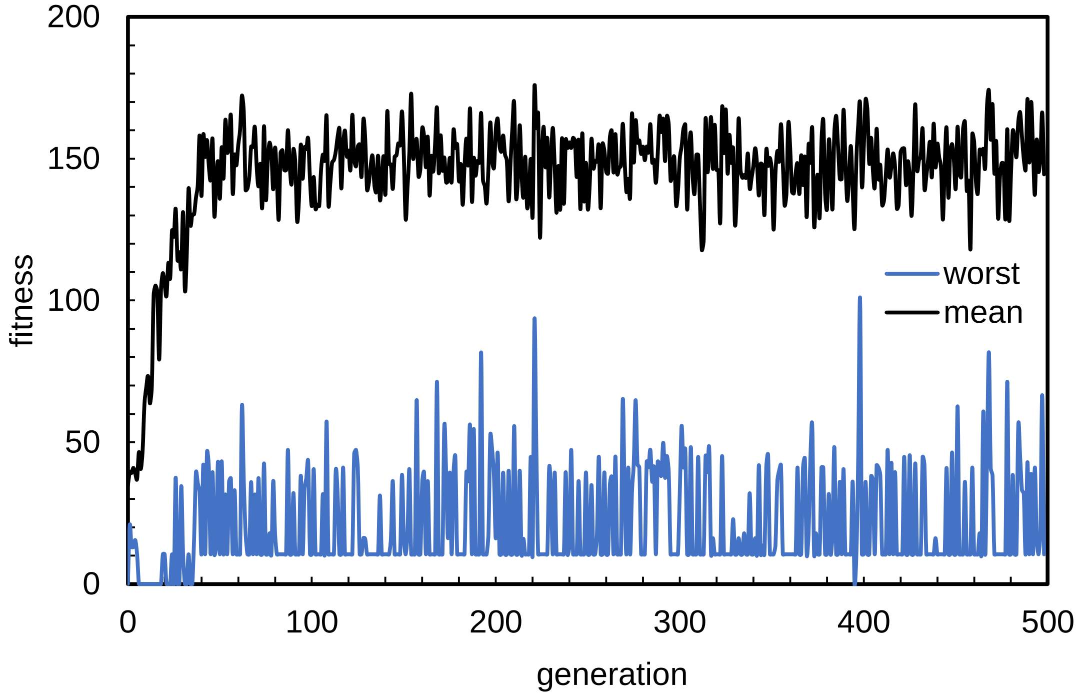


(b)

Figure S4. The evolution of mean (mean), maximum (max), and minimum (min) values of lnK_{ow} (a) and the mean and worse fitness (b) with generation in case 3 study.



(a)



(b)

Figure S5. The evolution of mean (mean), maximum (max), and minimum (min) values of lnK_{ow} (a) and the mean and worse fitness (b) with generation in case 3 study before SA.

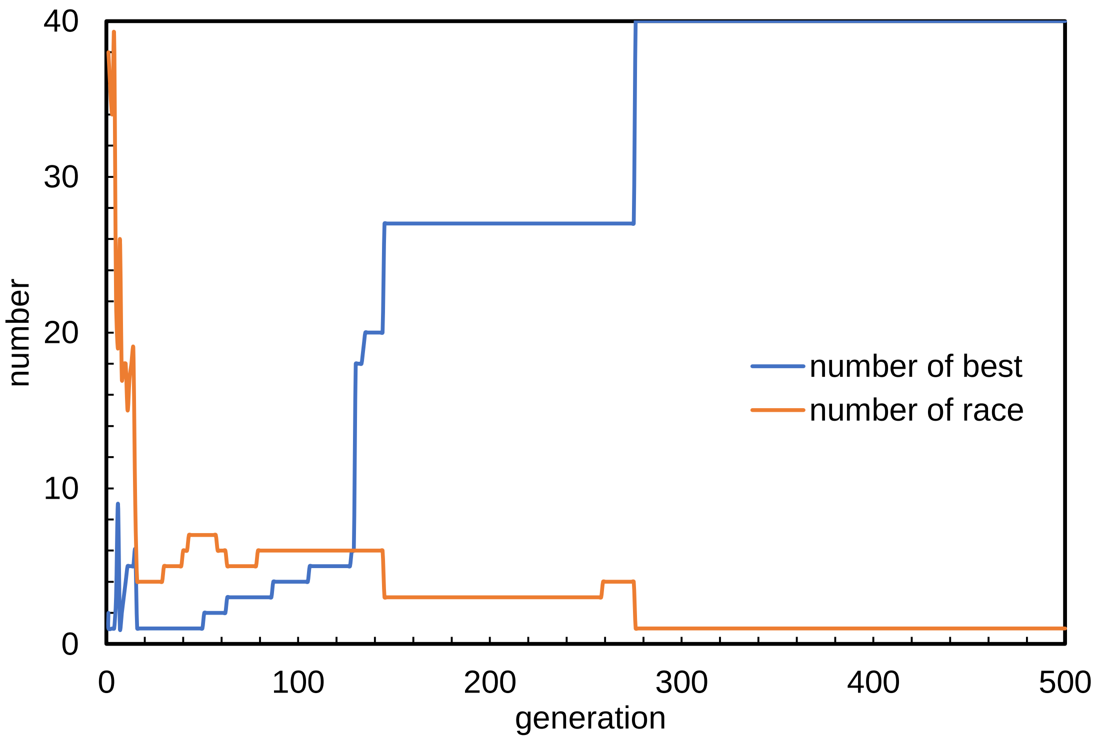


Figure S6. The number of best species and different species (races) in case 2.

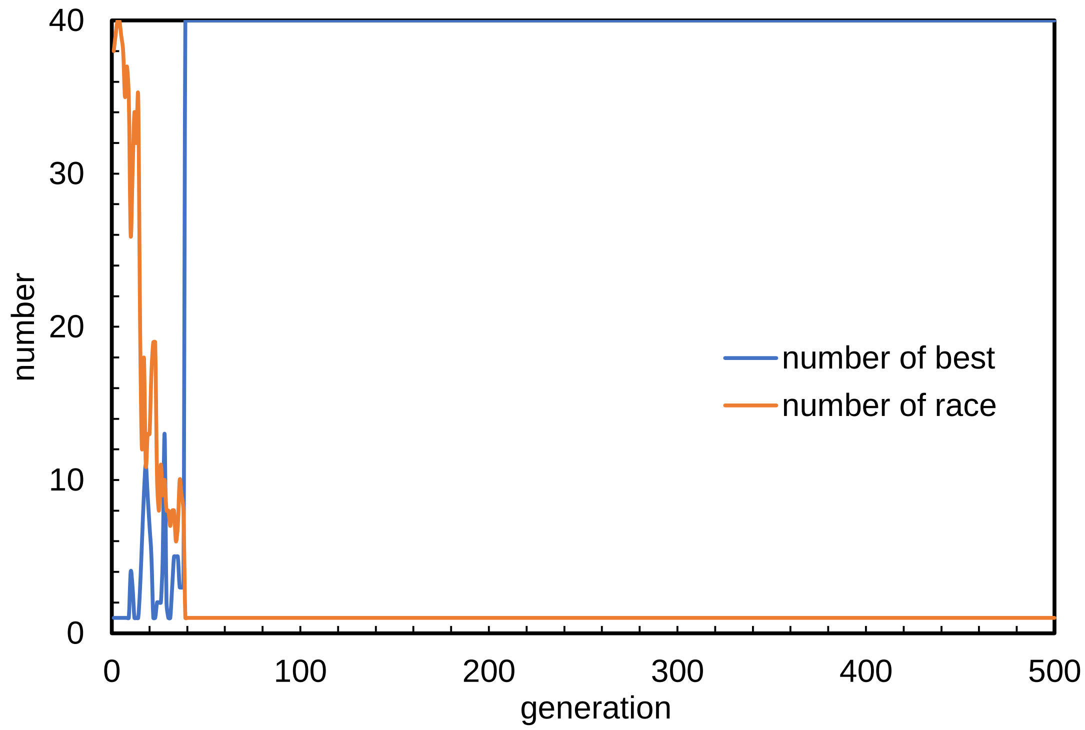


Figure S7. The number of best species and different species (races) in case 3.

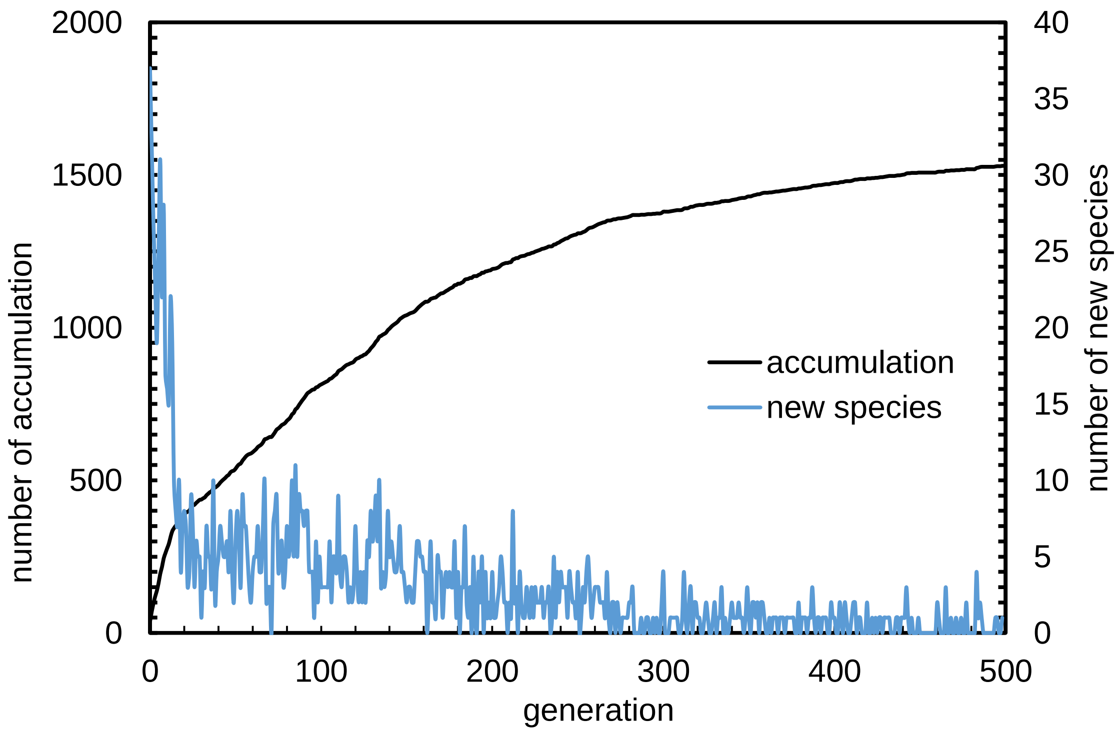


Figure S8. The number of new species created in each generation (blue line) and the accumulated number of new species (black line) for case 2.

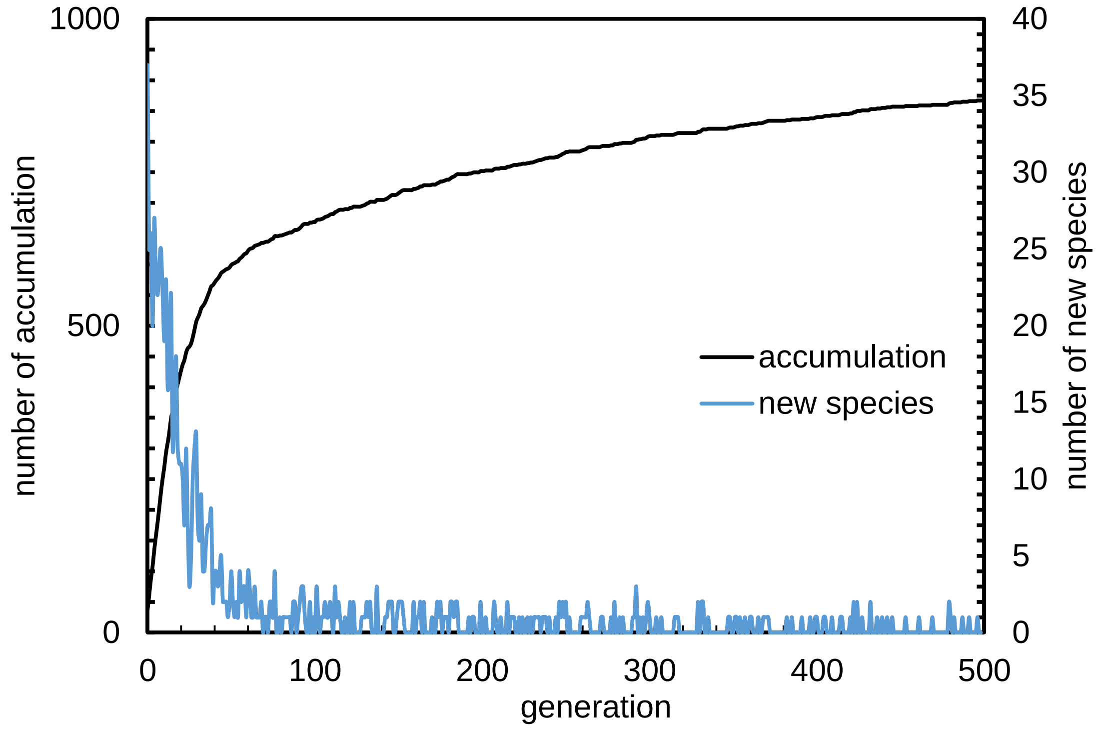
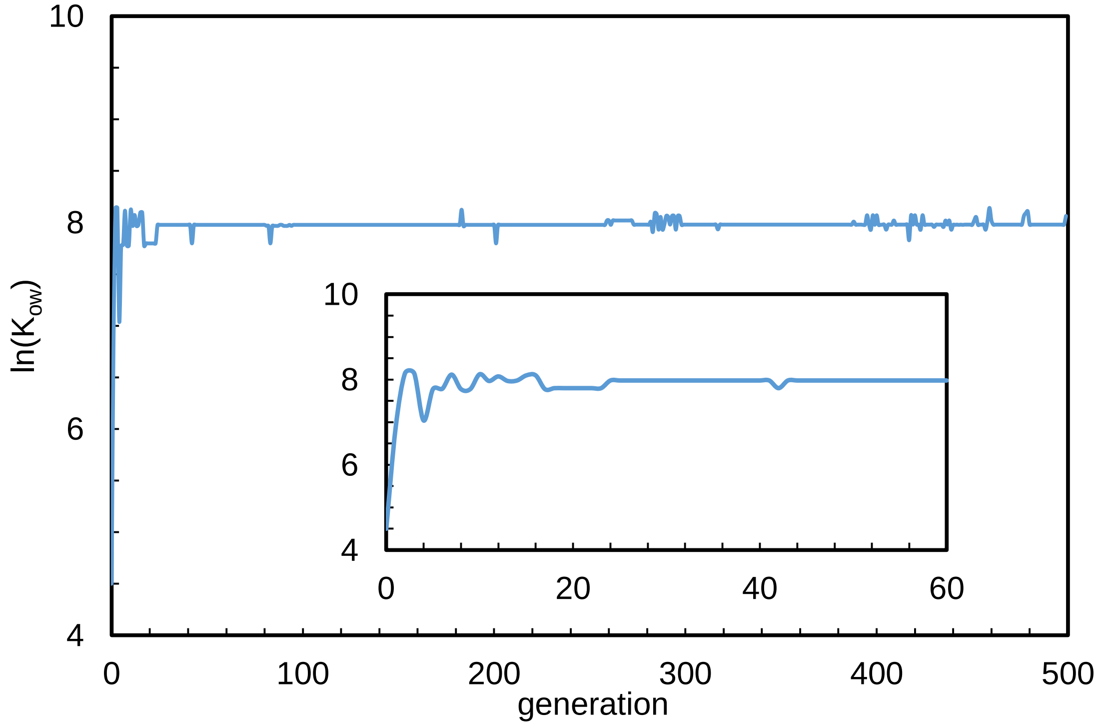
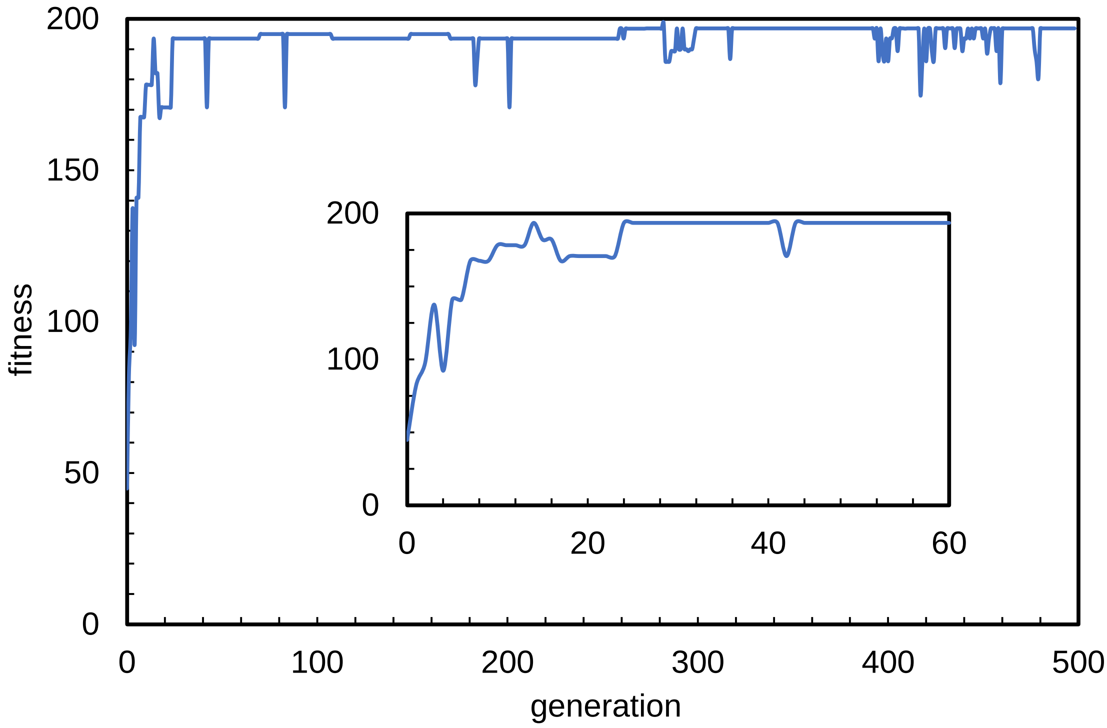


Figure S9. The number of new species created in each generation (blue line) and the accumulated number of new species (black line) for case 3.

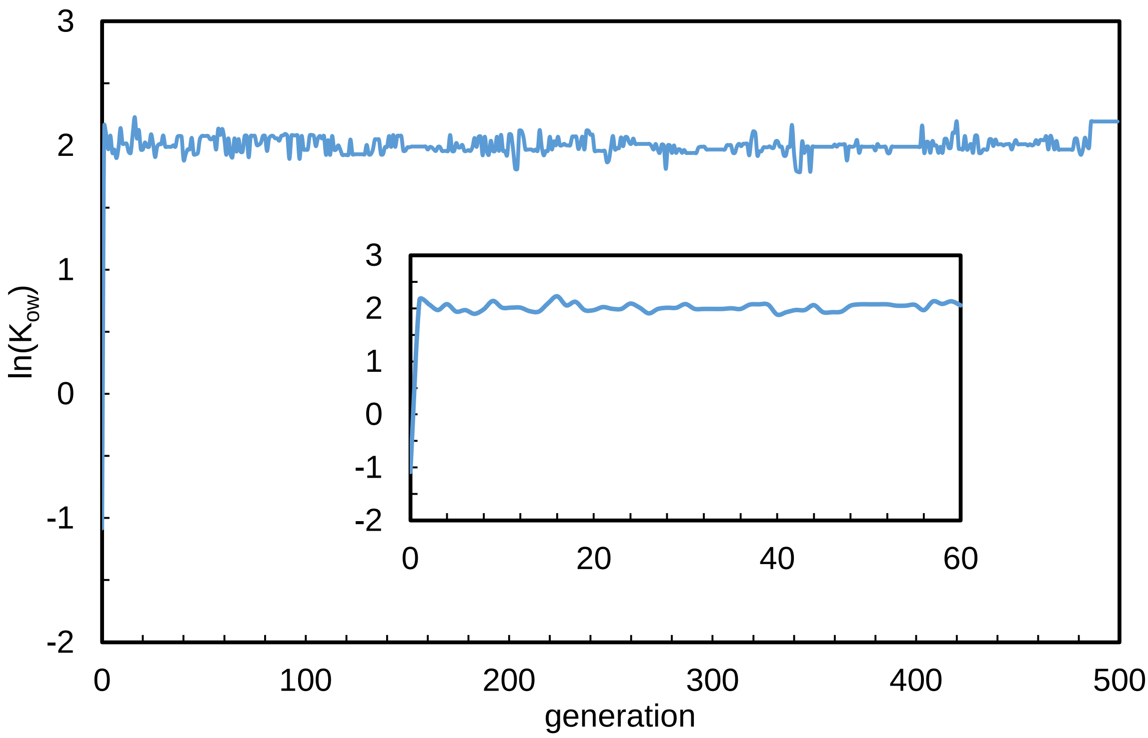


(a)

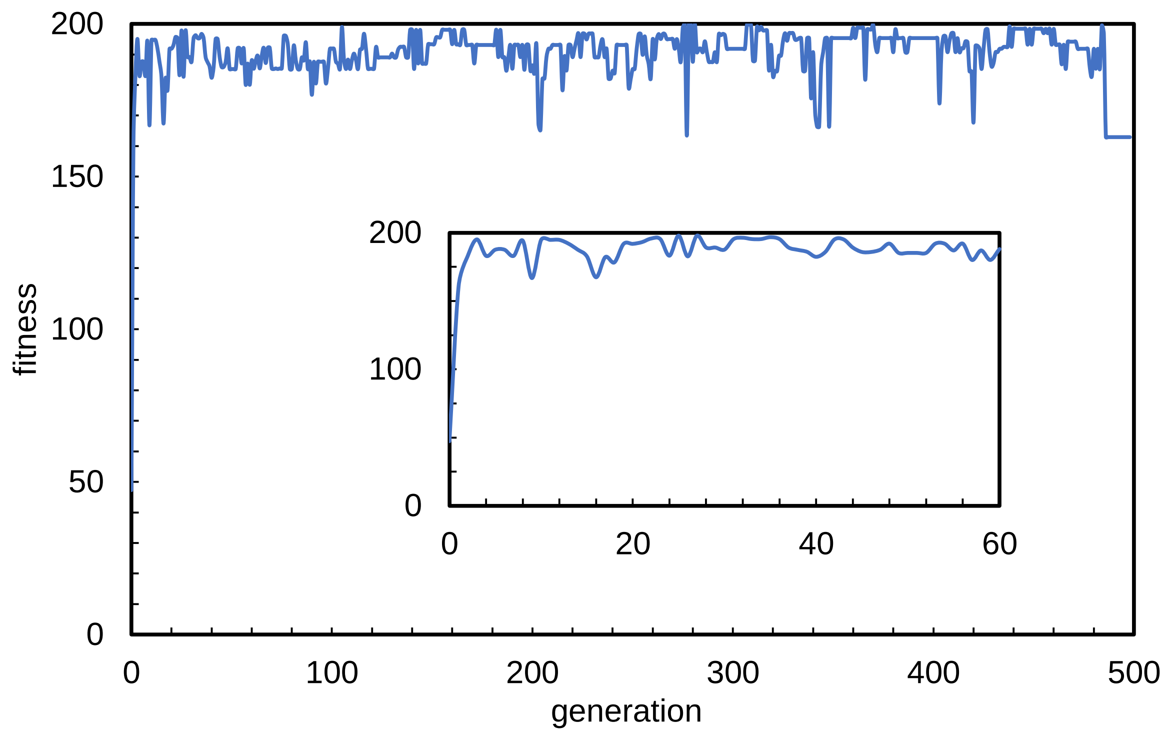


(b)

Figure S10. The best species of case 4 for GA with (a) $\ln K_{ow}$ and (b) fitness with generation.

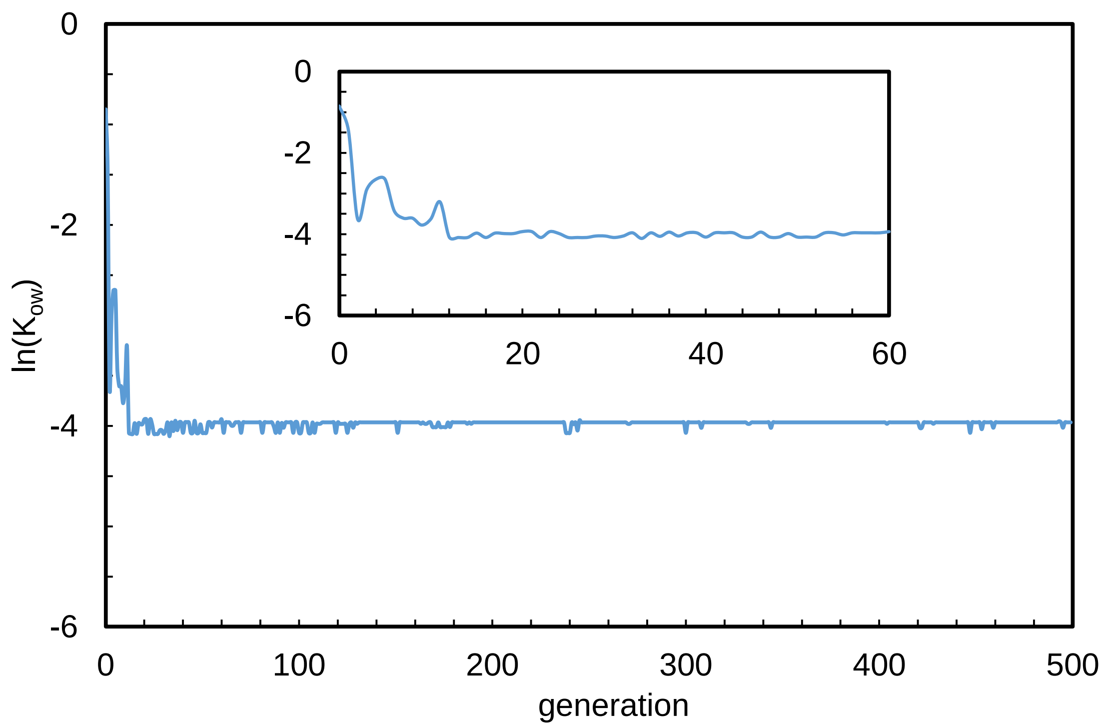


(a)

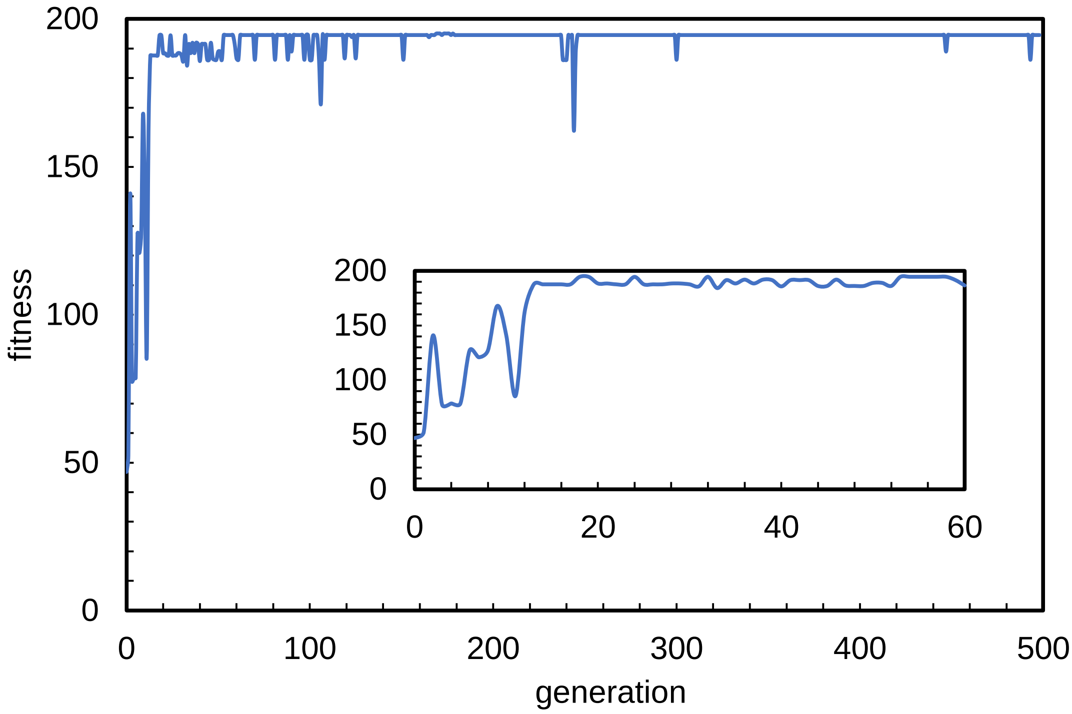


(b)

Figure S11. The best species of case 5 for GA with (a) lnK_{ow} and (b) fitness with generation.

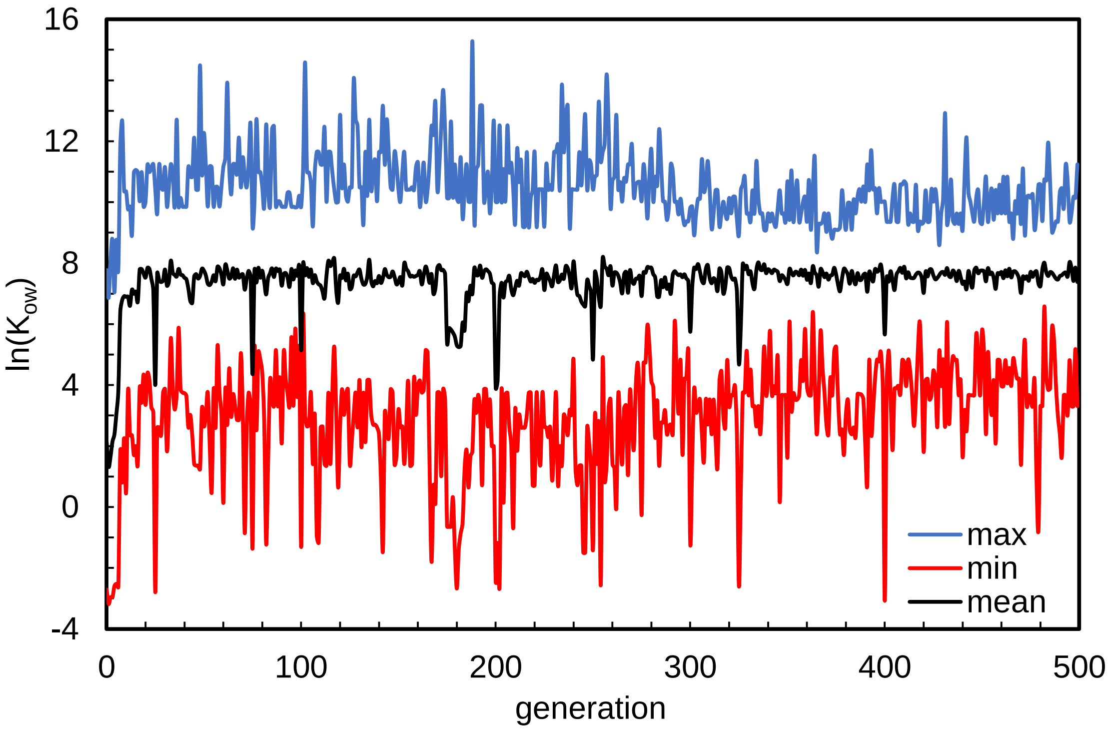


(a)

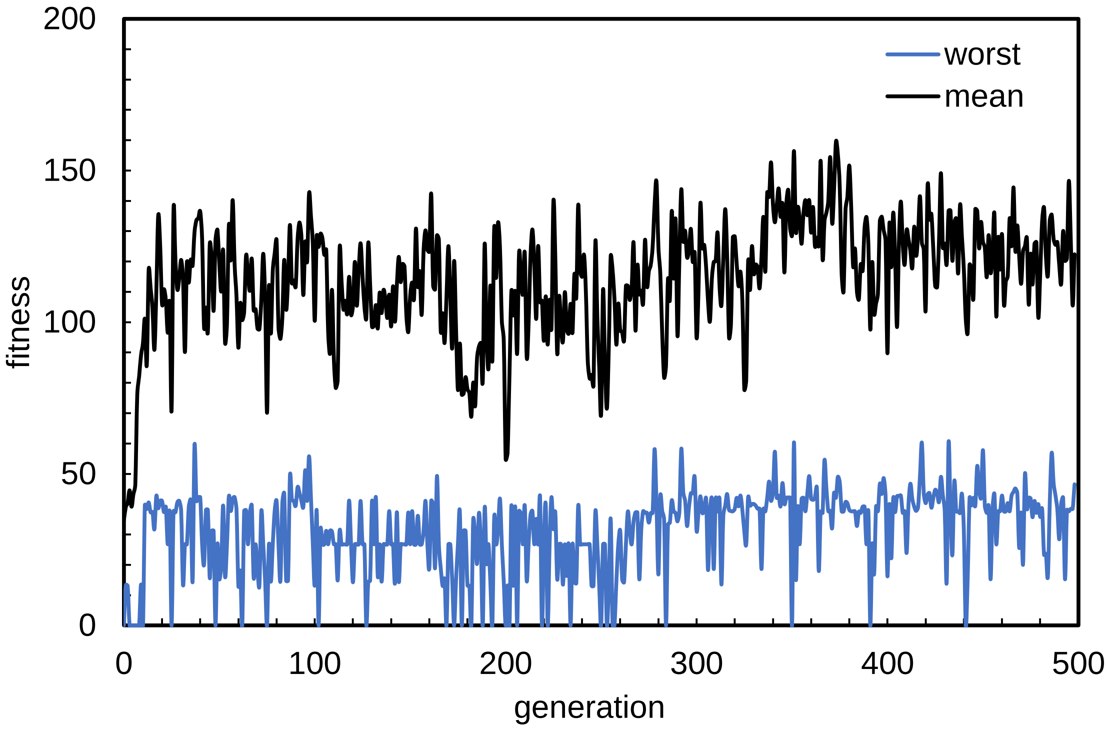


(b)

Figure S12. The best species of case 6 for GA with (a) $\ln K_{ow}$ and (b) fitness with generation.

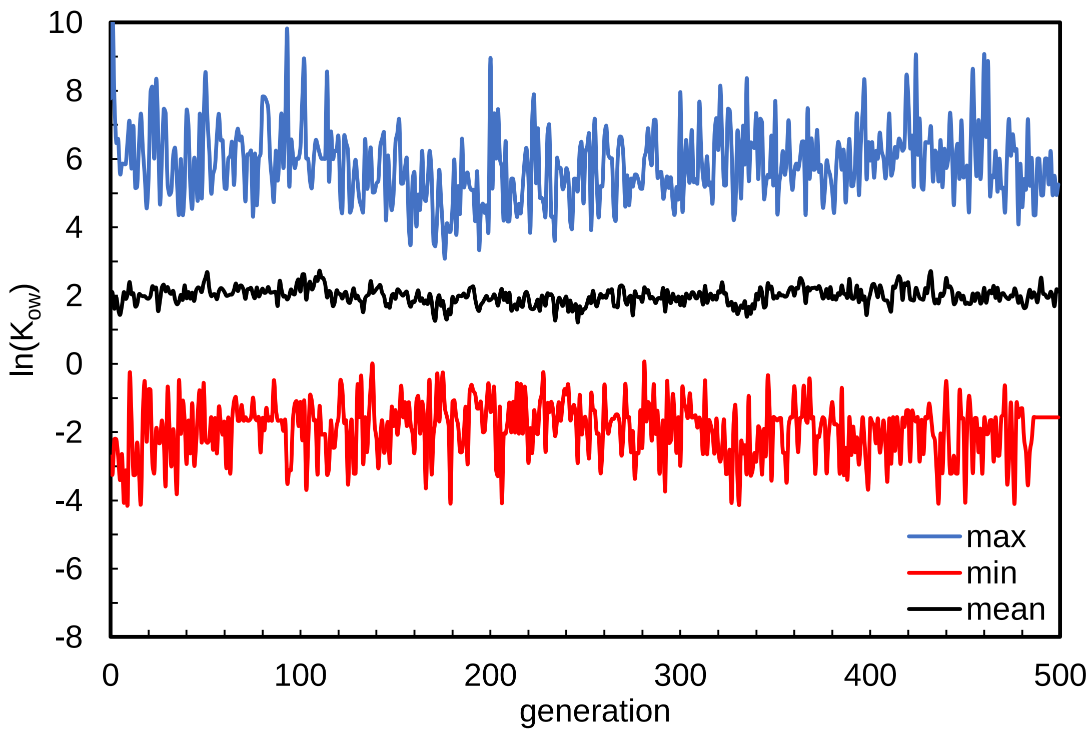


(a)

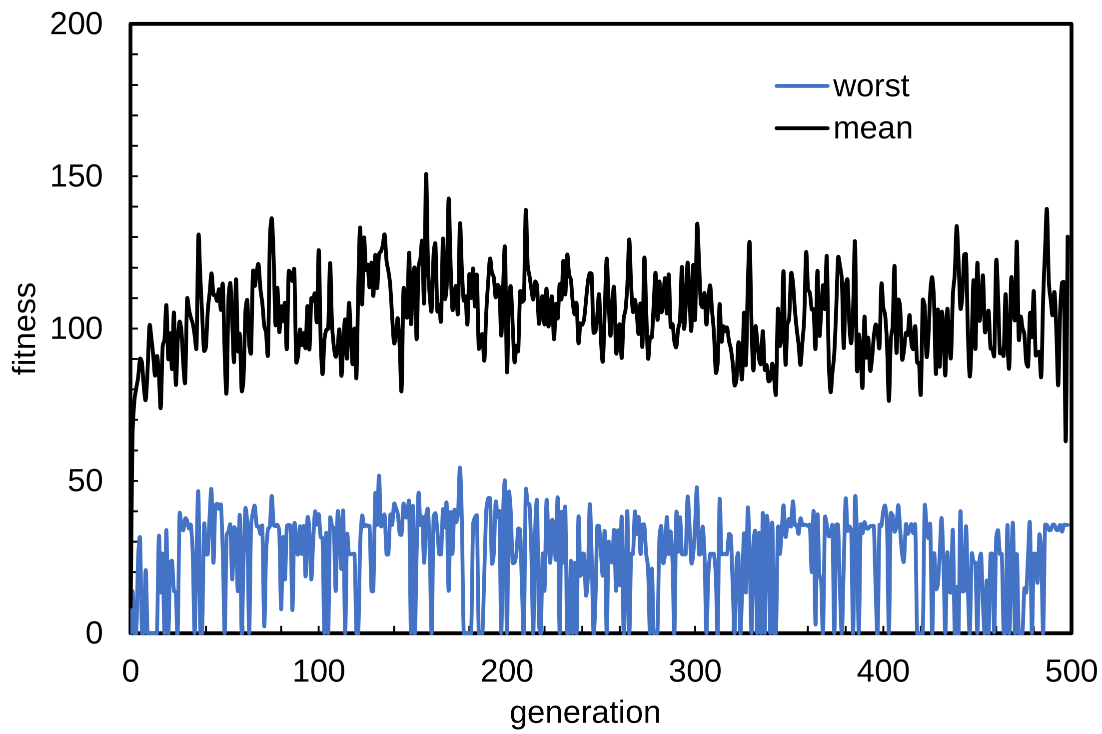


(b)

Figure S13. The evolution of mean (mean), maximum (max), and minimum (min) values of $\ln K_{ow}$ (a) and the mean and worse fitness (b) with generation in case 4 study with GA.

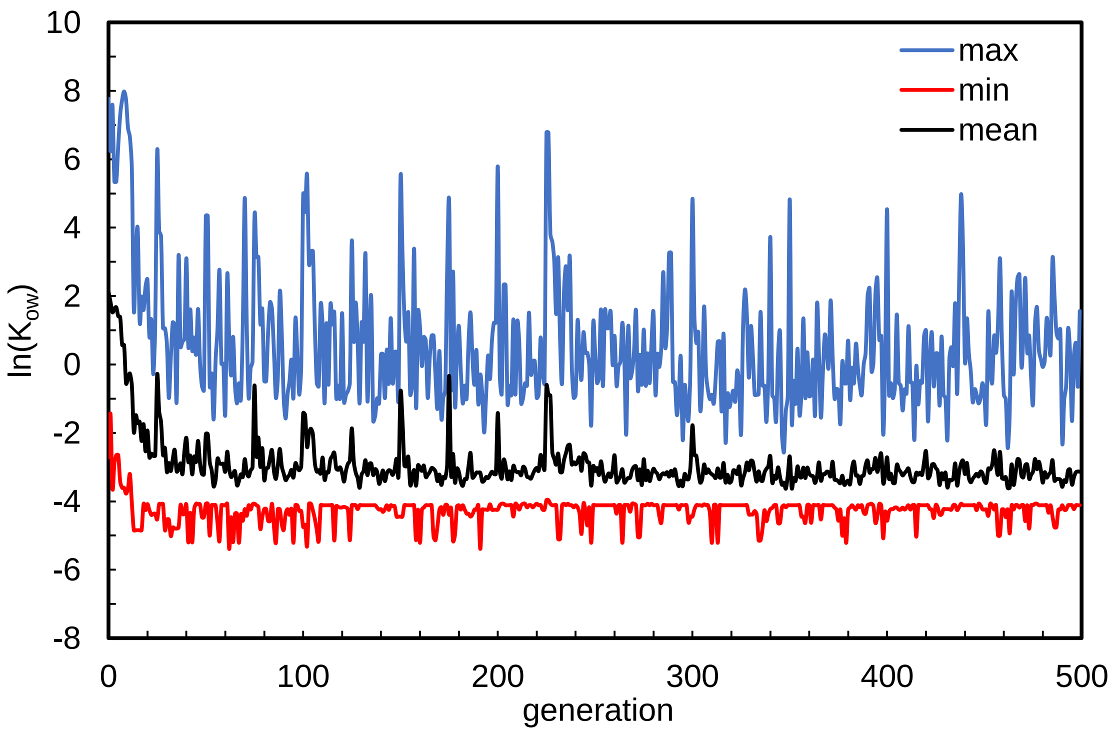


(a)

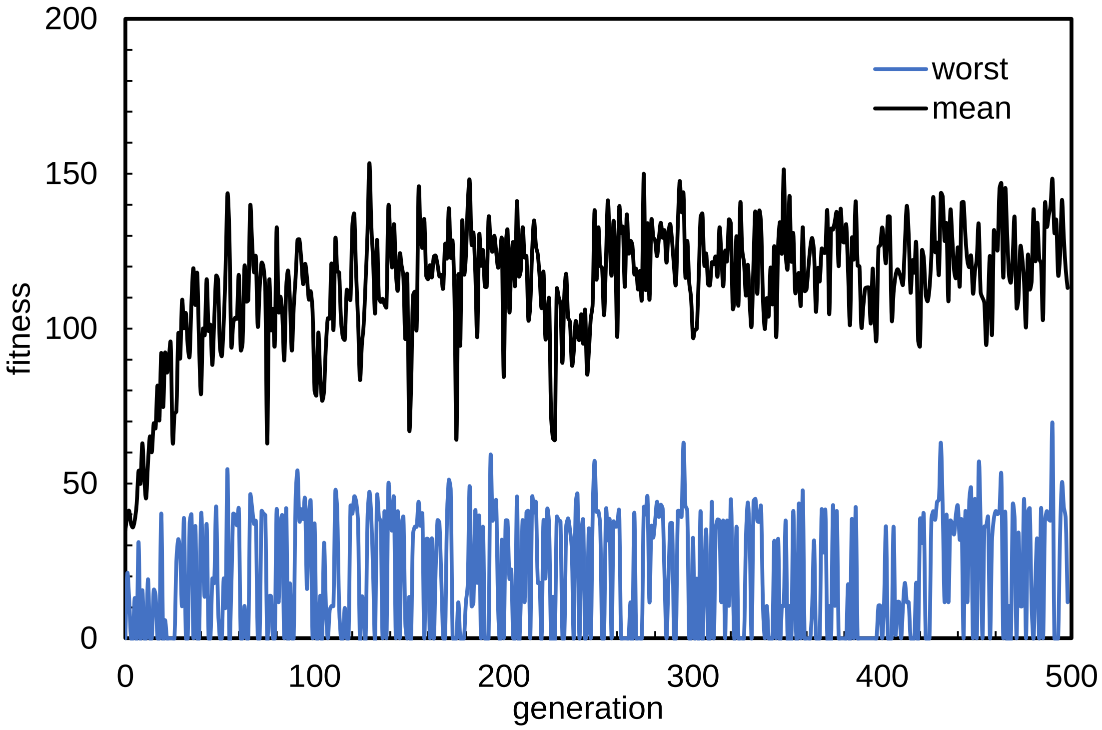


(b)

Figure S14. The evolution of mean (mean), maximum (max), and minimum (min) values of lnK_{ow} (a) and the mean and worse fitness (b) with generation in case 5 study for GA.



(a)



(b)

Figure S15. The evolution of mean (mean), maximum (max), and minimum (min) values of lnK_{ow} (a) and the mean and worse fitness (b) with generation in case 6 study for GA.

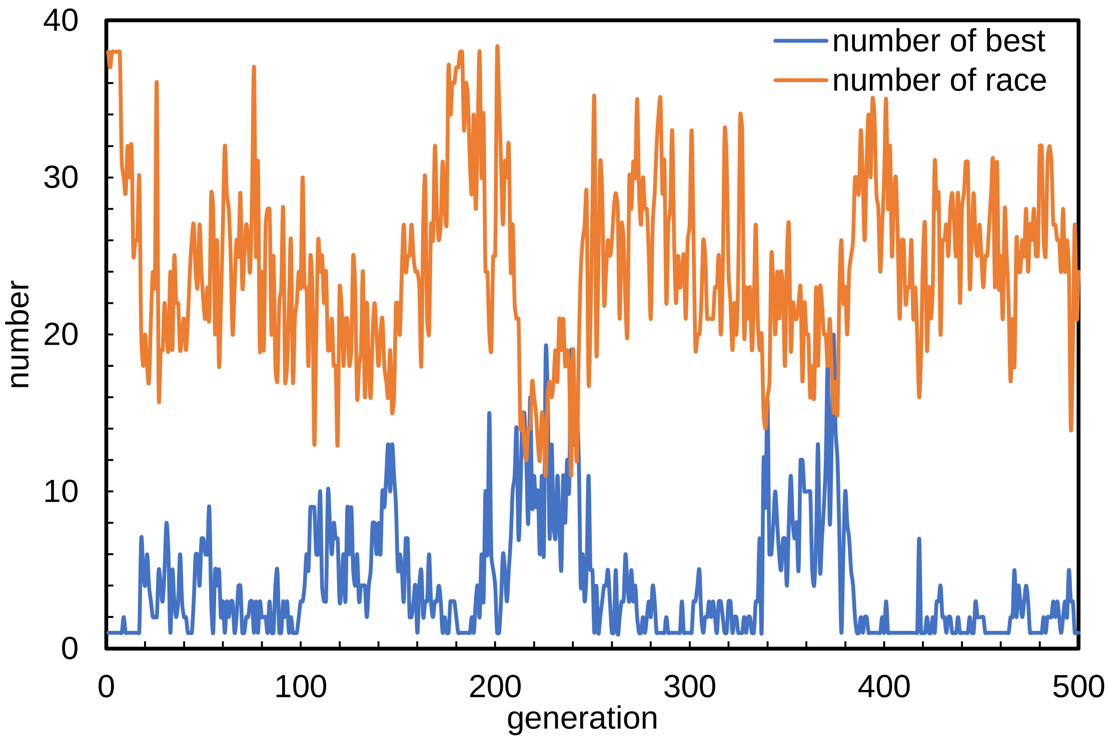


Figure S16. The number of best species and different species (races) for case 4 with GA.

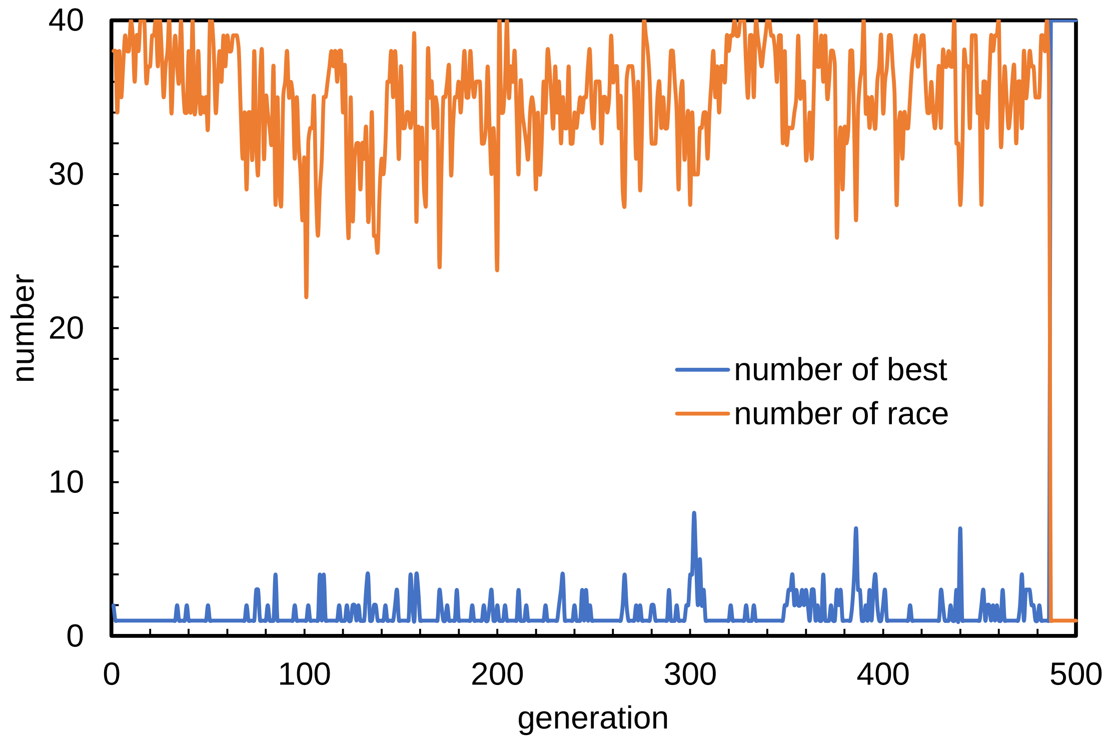


Figure S17. The number of best species and different species (races) for case 5 with GA.

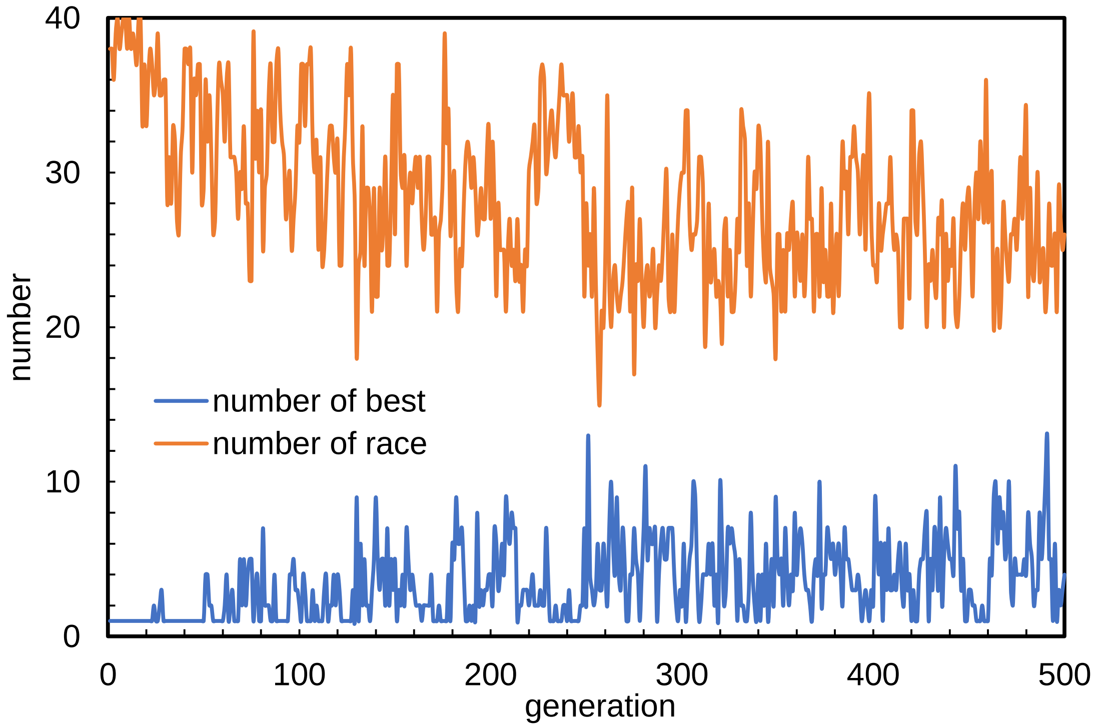


Figure S18. The number of best species and different species (races) for case 6 with GA.

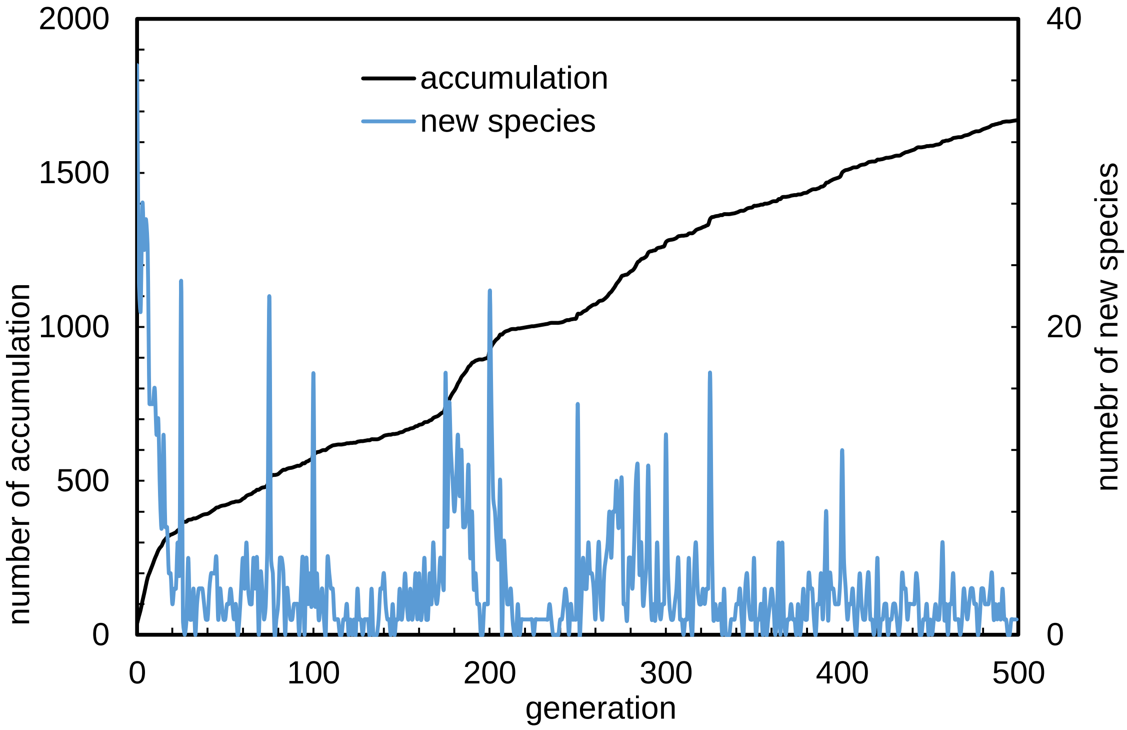


Figure S19. the accumulated number with generation and the new species created in each generation for case 4 with GA.

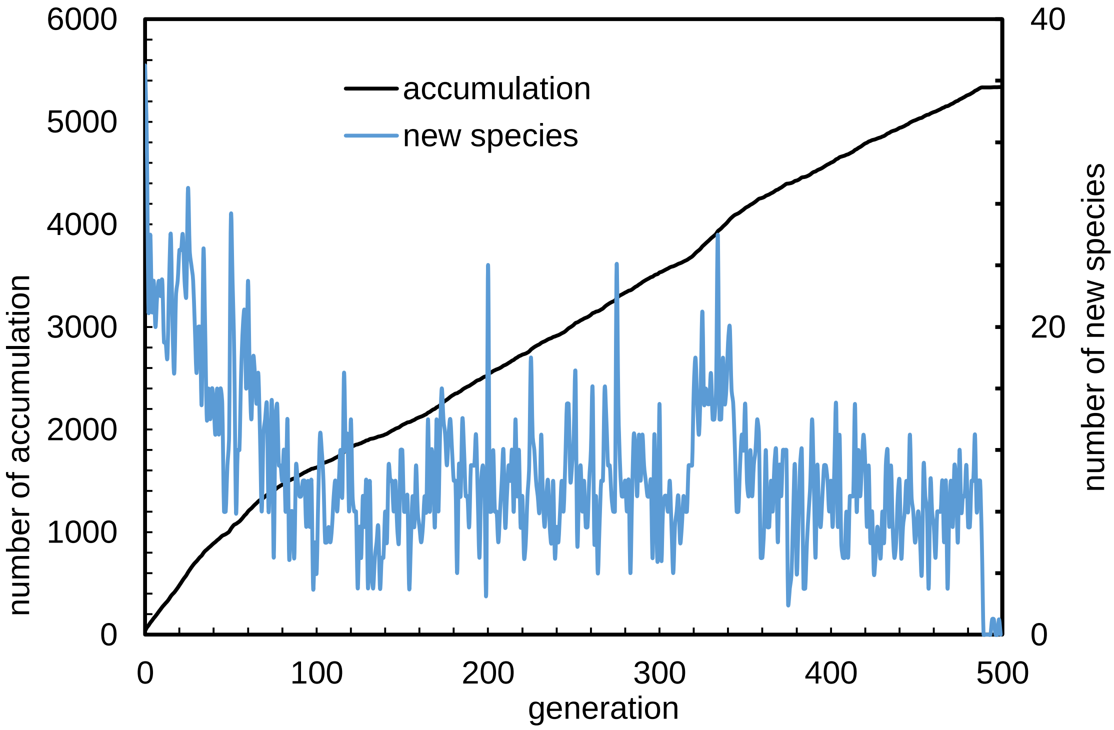


Figure S20. the accumulated number with generation and the new species created in each generation for case 5 with GA.

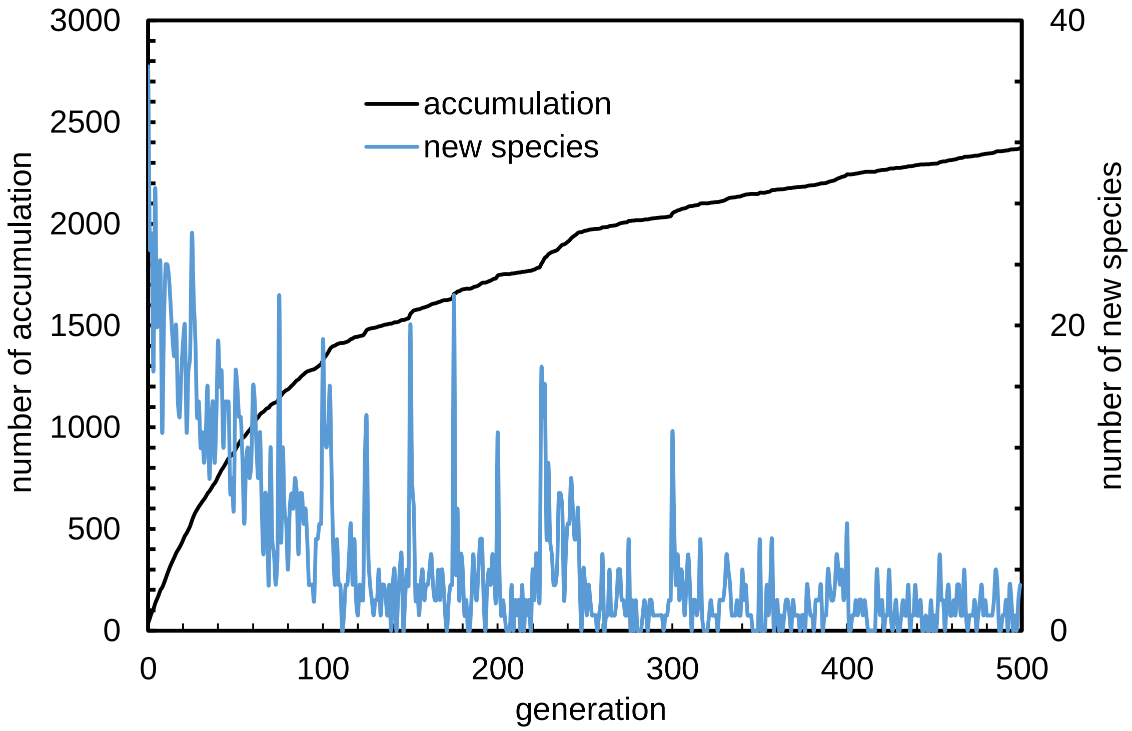


Figure S21. the accumulated number with generation and the new species created in each generation for case 6 with GA.

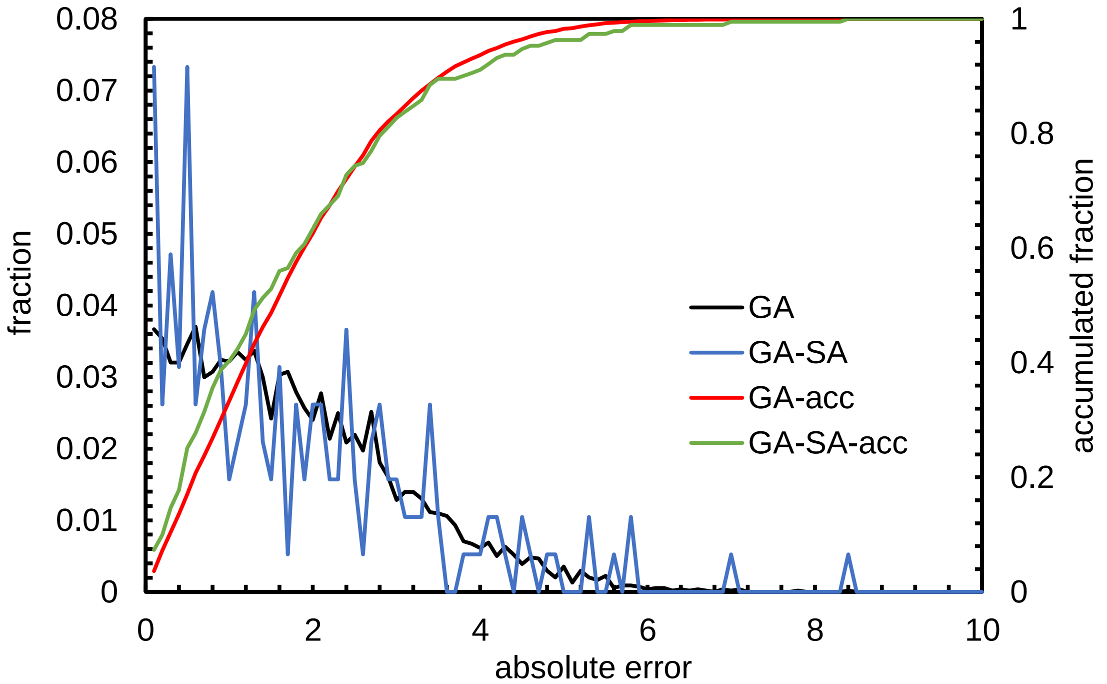


Figure S22. The fraction of the species in the absolute error range and the accumulation fraction in the range for GA-SA (case 2) and GA (case 5).

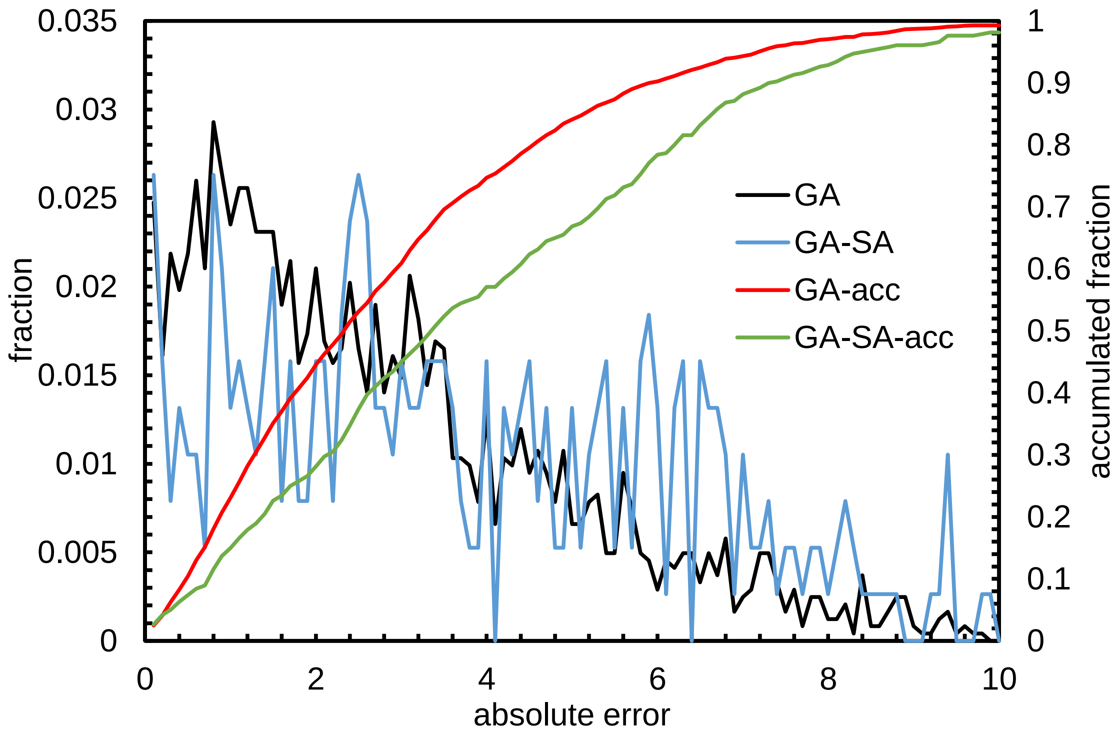


Figure S23. The fraction of the species in the absolute error range and the accumulation fraction in the range for GA-SA (case 3) and GA (case 6).

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