



THE CATHODIC CAGE PLATFORM IN SURFACE ENGINEERING

Renan Matos Monção¹ , Gabriely Gonçalves Lima¹ , Thercio Henrique de Carvalho Costa² , Romulo Ribeiro Magalhães de Sousa^{1,*}

1. Universidade Federal do Piauí – Pró-Reitoria de Pós-Graduação – Programa de Pós-Graduação em Ciências e Engenharia dos Materiais – Teresina (PI), Brazil.
2. Universidade Federal do Rio Grande do Norte – Centro de Tecnologia – Departamento de Engenharia Mecânica – Natal (RN), Brazil.

Corresponding author: romulorms@gmail.com

Section Editor: Mariana Fraga

Received: Nov. 20, 2025 **Approved:** Dec. 03, 2025

ABSTRACT

This review summarizes the development of cathodic cage plasma nitriding (CCPN) and cathodic cage plasma deposition (CCPD) techniques. CCPN was introduced to eliminate issues in direct current plasma nitriding (DCPN), such as the edge effect, by isolating the sample at a floating potential and using radiative heating. The process was further adapted for CCPD, in which the cage serves as a sputtering target (e.g., Ti, graphite, Mo, Hastelloy) for the deposition of ceramic and metallic films. Combining nitriding pretreatment with CCPD resulted in duplex treatments that establish a hardness gradient and enhance film adhesion. The most recent advance is cathodic cylinder plasma deposition (CCyPD), which employs compacted powder targets (such as MoS₂ or metal oxides) for composite film deposition and *in situ* oxide reduction. The review traces the evolution from process improvement to a versatile platform for surface engineering.

KEYWORDS: Cathodic cage, Plasma deposition, Surface engineering.

A TÉCNICA DE GAIOLA CATÓDICA NA ENGENHARIA DE SUPERFÍCIES

RESUMO

Este artigo de revisão apresenta a trajetória evolutiva da técnica de nitretação e deposição a plasma por gaiola catódica. O ponto de partida foi a nitretação a plasma em gaiola catódica [*cathodic cage plasma nitriding* (CCPN)], desenvolvida para solucionar limitações crônicas da nitretação a plasma convencional [*direct current plasma nitriding* (DCPN)], como o “efeito de borda”, isolando a amostra em potencial flutuante e utilizando aquecimento radiativo. A técnica evoluiu naturalmente para a deposição a plasma em gaiola catódica [*cathodic cage plasma deposition* (CCPD)], na qual a própria gaiola começou a ser utilizada como alvo de pulverização (*sputtering*) (ex.: Ti, grafite, Mo, Hastelloy) para depositar filmes cerâmicos e metálicos. A combinação da nitretação, como pré-tratamento, com a deposição (CCPD) levou ao desenvolvimento dos tratamentos duplex, criando um gradiente de dureza favorável que resolve os problemas de adesão de filmes duros. A inovação mais recente é a deposição a plasma por cilindros catódicos [*cathodic cylinder plasma deposition* (CCyPD)], uma nova configuração de deposição que utiliza alvos de pó compactado (como MoS₂ ou óxidos metálicos), permitindo a deposição de compósitos e a redução de óxidos *in situ*. Esta revisão documenta a evolução de uma solução de processo para uma plataforma de engenharia de superfícies robusta e versátil.

PALAVRAS-CHAVE: Gaiola catódica, Deposição a plasma, Engenharia de superfícies.

INTRODUCTION

The problem of conventional nitriding and the cathodic cage plasma nitriding (CCPN)

Plasma-based materials processing is a cornerstone of modern surface engineering. Direct current plasma nitriding (DCPN) is a consolidated thermochemical method for hardening steels. However, the conventional DCPN configuration possesses intrinsic electrodynamic limitations arising from the use of the workpiece as the cathode. In components with complex geometries, the electric field distribution concentrates at sharp edges and corners, significantly increasing the local ion current density. This phenomenon, known as the edge effect, leads to localized overheating and preferential sputtering, degrading surface integrity. Furthermore, in cavities with dimensions comparable to the cathode dark space, the overlapping of the Debye sheaths triggers the hollow cathode effect directly on the workpiece, resulting in uncontrolled temperature spikes and arcing.¹

To overcome these physical constraints, the CCPN process was developed.¹ The fundamental innovation of CCPN lies in the decoupling of the plasma generation from the thermal diffusion process. By isolating the sample at a floating potential, the formation of a high-voltage collision sheath on the sample surface is suppressed. Instead, the plasma density is concentrated on the cage walls (the actual cathode). Consequently, the sample heating mechanism shifts from kinetic energy transfer (ion bombardment) to thermal radiation and convection from the heated cage. This radiative equilibrium ensures an isotropic temperature distribution regardless of sample geometry, effectively neutralizing the geometric dependence of the electric field.

Comparative studies have validated this mechanism, showing the complete elimination of erosion rings,¹ as illustrated in Fig. 1, and thermal gradients in samples of varying dimensions.² With the stabilization of the thermodynamic parameters, research evolved to optimize the chemical potential of the atmosphere, enabling fine control over phase formation, such as the S-phase in stainless steels.³

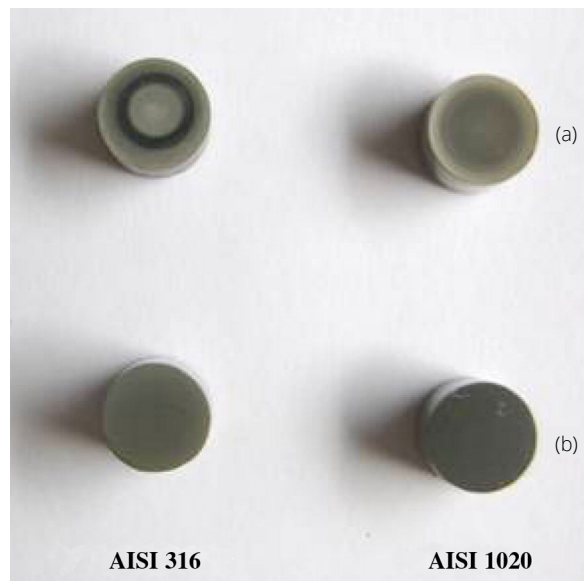


Figure 1: Comparison of the surface finish of steel samples. (a) The result of DCPN exhibits “erosion rings” (edge effect). (b) CCPN demonstrates the complete elimination of surface defects.

Source: Alves et al.¹ Reprinted with permission from Elsevier.

Superior thermal control was confirmed by simultaneously treating AISI 1020 steel samples of varying heights (1 mm to 10 mm). All samples showed identical compound-layer thickness and surface microhardness, indicating that the thermal gradient had been eliminated.² Industrial tests applying CCPN to AISI 4340 steel cutting blades showed a 58% to 74% increase in tool life, demonstrating the method’s effectiveness for complex geometries.⁴

With a uniform treatment mechanism established, research focused on process optimization, notably by adjusting the N_2/H_2 gas mixture ratio.³ This enabled fine control over phase formation, such as the S-phase (expanded austenite) in stainless steels, and allowed for the simultaneous optimization of hardness (up to 1,100 HV), layer thickness (31.6 μm), and corrosion resistance.³

Mastery of the nitriding process (CCPN) was, however, only the starting point. The observation that sputtering of the cathodic cage was an inherent and controllable mechanism led to the technique's primary transition: from a solution for uniform nitriding to a versatile platform for physical vapor deposition (PVD). This review presents the evolutionary trajectory of this technique, documenting its progression from CCPN to cathodic cage plasma deposition (CCPD),⁵ its consolidation through duplex treatments,⁶ and its most recent innovation: the development of cathodic cylinder plasma deposition (CCyPD).^{7,8}

The transition to physical deposition (CCPD): the cage as a sputtering target

Mastery of the CCPN process revealed that cage material sputtering was a fundamental mechanism. Even under nitriding conditions, ions such as Cr, Ni, and Mo from Hastelloy or stainless-steel cages were transferred to the sample surface.⁹ This observation led to the technique's primary evolution: the shift from a thermochemical diffusion process (CCPN) to a PVD approach, termed CCPD.^{5,10}

In this new configuration, the cathodic cage serves as a sputtering target to provide the deposition material, rather than acting solely as an electrode for plasma activation. The core experimental setup remains the same: the sample is positioned at a floating potential and is electrically isolated from the cathode.^{5,11,12}

The viability of this transition was validated by using cages made from the desired target material instead of steel. Thin TiN and TiO_2 films were successfully deposited on silicon substrates using a grade 2 titanium cage.⁵ Figure 2 provides a cross-sectional micrograph confirming the uniform film formation achieved by this method.

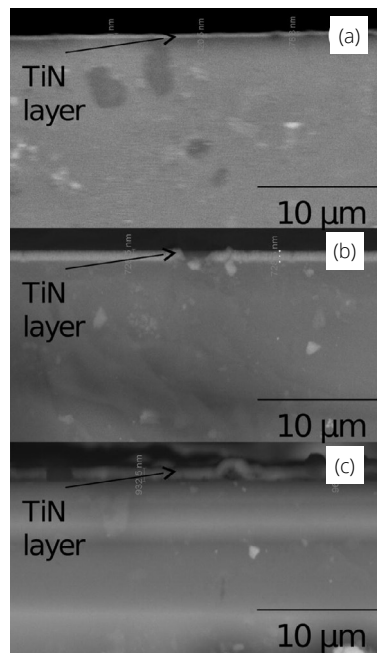


Figure 2: Cross-sectional scanning electron microscopy (SEM) micrograph of a TiN film deposited on a silicon substrate. The image confirms the feasibility of the CCPD technique for forming uniform films, validating the use of the titanium cage as a sputtering target. Scale bar: 10 μm .

Source: Sousa et al.⁵ Reprinted with permission from AVS Publishing.

The versatility of the CCPD platform was rapidly demonstrated through the deposition of additional films of industrial significance:

- Diamond-like carbon (DLC) films: using a graphite cage, an amorphous carbon coating with crystalline DLC islands was obtained, exhibiting hardness up to 1,300 HV.¹⁰
- Metal oxides: using a molybdenum cage, a molybdenum oxide (MoO_3) film was synthesized.¹¹
- Alloy films: using a Hastelloy C-276 cage, films containing FeNi_3 , CrNi, and MoN were deposited for high-corrosion-resistance applications.⁹

A critical contribution of this research was the investigation of the sample's electrical potential on the deposition mechanism, comparing the floating potential (CCPD method) with the cathodic potential (conventional method). The results demonstrated that floating potential is fundamental for depositing pure films. In MoO_3 deposition, the floating potential sample yielded a pure MoO_3 film, whereas the cathodic potential sample produced a mixed film contaminated with iron oxides (Fe_2O_3) and intermetallic phases (Fe_2Mo_3 , Fe_3Mo), originating from sputtering of the steel substrate itself.¹¹ Identical results were obtained for TiN deposition on eutectoid steel (AISI 1080): the floating potential sample (F-75H) showed dominant TiN formation, achieving maximum hardness (1,100 HV) and the lowest wear volume, while the cathodic potential sample (C-75H) was dominated by iron nitrides (Fe_2N , Fe_4N), resulting in lower hardness (~ 460 HV).¹²

These findings established that CCPD at floating potential is an effective technique for depositing pure films via cage sputtering, with radiative heat from the cage promoting diffusion and film adhesion.

Process synergy: duplex treatments for interface optimization

The development of uniform nitriding (CCPN) and film deposition (CCPD) enabled the implementation of duplex treatments. Direct deposition of hard ceramic films (PVD/CVD) onto softer steel substrates often leads to the “egg-shell effect,” in which insufficient mechanical support causes coating fracture, delamination, and early failure.⁶

A nitriding pre-treatment was combined with CCPD to overcome this challenge. In a key study on AISI M2 high-speed steel, CPN was first used to create a deep diffusion zone, followed by TiN deposition via CCPD. This sequence established a favorable hardness gradient, thereby increasing the substrate's load-bearing capacity and enhancing film adhesion.⁶ Figure 3 illustrates the resulting duplex microstructure.

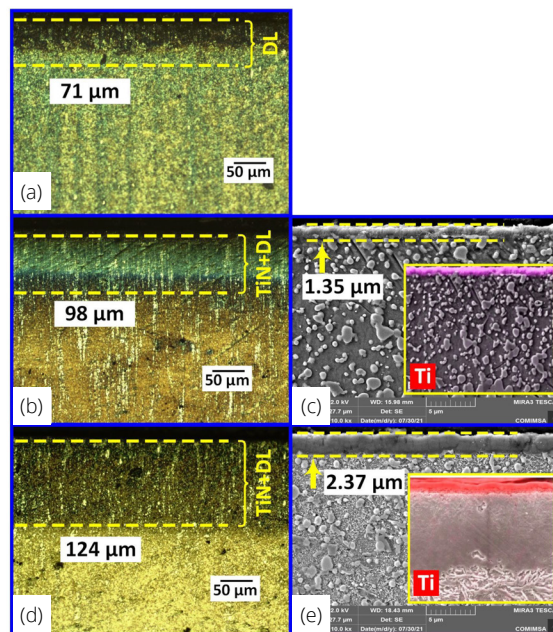


Figure 3: Cross-sectional SEM analysis of duplex-treated AISI M2 steel. The image (e) shows the combined layer (TiN + DL), where the 124 μm diffusion layer (DL) formed by pre-nitriding provides mechanical support for the 2.37 μm TiN film. Scale bar: 50 μm .

Source: Abreu et al.⁶ Published under a Creative Commons (CC BY) license.

This synergy was confirmed in AISI 1045 steel, where a duplex treatment of PN followed by vanadium cage deposition (CCPD) produced a nitrided layer that acted as mechanical support for the vanadium nitride film. This resulted in a surface hardness of 885 HV, a 77% increase compared to nitriding alone (499 HV).¹³ The process flexibility was also demonstrated by reversing the order: a Hastelloy cage deposition (containing Cr, Mo, Ni) followed by post-nitriding increased hardness from 346 HV to 1,692 HV and produced a deep diffusion zone.¹⁴

For non-alloyed steels (St-37), which respond poorly to conventional nitriding, an innovative duplex treatment using two CCPD steps was applied. The first step involved deposition from an aluminum cage, followed by a second deposition with a stainless-steel cage. The deposited aluminum enabled the formation of aluminum nitride (AlN), increasing the hardness to approximately 1,124 HV, a value not achievable by conventional methods for this steel.¹⁵

However, this research also defined the technique’s boundaries. When duplex treatment (vanadium deposition followed by nitriding) was tested on aluminum alloys (AA1050), the subsequent nitriding step proved detrimental, reducing the vanadium layer thickness (from 7.6 μm to 3.2 μm) and decreasing wear resistance. This result indicates that the duplex technique is not universally applicable to non-ferrous substrates.¹⁶ The duplex approach thus consolidated the CCPD platform as an effective method for engineering hardness gradients to optimize the tribological performance of tool steels and special alloys.

Critical analysis and limitations of the cathodic cage platform

To provide a balanced scientific framework, it is essential to analyze the operational limitations and material-specific boundaries of the platform. While versatile, the technique has constraints. A primary limitation is the deposition rate in CCPD, which is generally lower than in directed magnetron sputtering due to the omnidirectional nature of the cage sputtering and the diffusive transport of species to the floating substrate.¹⁷

Furthermore, the thermal operational envelope is critical. For substrates where corrosion resistance is paramount, such as AISI 316L, process temperatures must be strictly controlled (typically below 450 °C) to avoid chromium nitride precipitation, which degrades the passive layer.⁹ The duplex treatment approach also has material limitations; for instance, applying a post-nitriding step to vanadium-coated AA1050 aluminum alloy proved detrimental, reducing the coating thickness and wear resistance, indicating that the duplex strategy is not universally applicable to non-ferrous substrates.¹⁶

Ideally, the selection between conventional and cathodic cage techniques should be based on the specific physical requirements of the application. Table 1 provides a conceptual comparison to guide this selection.

Table 1: Comparative analysis of physical mechanisms and operational characteristics of plasma techniques.

FEATURE	DCPN	CCPN	CCPD
Primary plasma source	Workpiece surface	Metallic cage surface	Cage surface (target)
Sample potential	Cathodic (negative bias)	Floating (electrically isolated)	Floating (electrically isolated)
Heating mechanism	Direct ion bombardment (kinetic)	Thermal radiation (radiative)	Thermal radiation (radiative)
Dominant mechanism	Diffusion	Diffusion	Sputtering + deposition
Main limitation	Edge effect/overheating	Limited to thermochemical treatment	Deposition rate (vs. magnetron)

Source: Elaborated by the authors

The research frontier: the cathodic cylinder (CCyPD) arrangement and emerging applications

Recent work on the CCPD platform has removed the need to fabricate the entire cage or lid from the target material. Changes to the experimental setup have increased material flexibility, enabling the deposition of composites and solid lubricants and the use of low-cost precursors.

A modular approach was first used, with a molybdenum cage body and interchangeable lids made from metals such as titanium, steel, or copper. In an oxidizing atmosphere, this setup allowed the synthesis of complex oxide coatings containing Mo, Cu, Ti, and Fe. The film composition depended on the combination of materials in the lid and cage body.¹⁸

This modular target concept resulted in the development of CCyPD, a patented arrangement. In CCyPD, the cage or its lid is modified to hold compacted powder cylinders of the deposition material.^{7,8} Figure 4 shows this configuration.

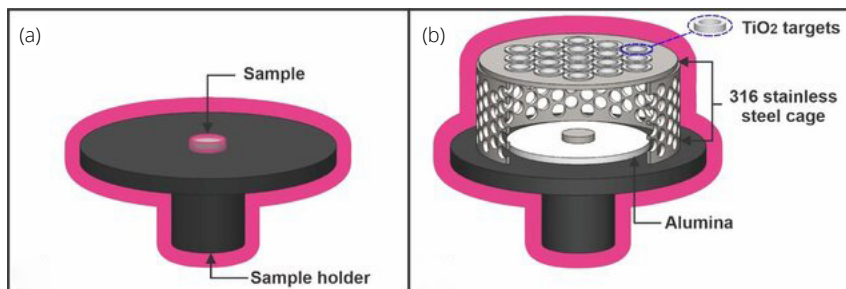


Figure 4: Schematic of the modified experimental arrangement (CCyPD) for deposition from powders. The configuration shows the insertion of targets (compacted TiO_2 nanoparticles or MoS_2 cylinders) into the cage lid, enabling the deposition of composites and non-machinable materials.

Source: Sampaio et al.¹⁹ Published under a Creative Commons (CC BY) license.

The Cathodic cylinder solved two main challenges. First, it allowed deposition of materials that cannot be easily machined into a cage, such as solid lubricants. For example, MoS_2 films deposited from compacted powder cylinders produced lubricant coatings with much lower wear.⁷

Second, CCyPD made it possible to use low-cost metal oxide precursors, such as Nb_2O_5 and TiO_2 , instead of pure metals. In a hydrogen-rich atmosphere, the plasma reduces these oxides during sputtering.⁸ The resulting metal atoms (Nb, Ti) react with carbon from graphite to form hard carbide films (TiC, NbC), increasing hardness (above 900 HV) and wear resistance.⁸

A similar method used TiO_2 nanoparticle targets together with a nitriding pre-treatment (duplex treatment). This approach allowed deposition on AISI 304 steel, producing films with high hydrophilicity and antibacterial activity, which are promising for biomedical applications.¹⁹

The technique has also been applied to non-metallic substrates. For temperature-sensitive materials such as cotton fabric, the reactor was modified by placing compacted ZnO rings as targets in the cage, and the fabric samples were positioned on the reactor lid, away from the dense plasma, to prevent thermal damage. This process deposited ZnO onto the fabric, giving it high photocatalytic and antibacterial properties.²⁰

CONCLUSIONS AND FUTURE PERSPECTIVES

The evolution of the cathodic cage platform represents a paradigm shift in surface engineering, transitioning from a specific problem-solving technique for nitriding geometries to a broad-spectrum system for material synthesis. Our analysis highlights that the fundamental innovation, the electrical decoupling of the substrate via floating potential, did more than solve the edge effect; it unlocked a new regime of plasma processing where sputtering (from the cage) and diffusion (on the substrate) can be independently controlled.

Critically, the transition from CCPN to CCPD and the recent CCyPD demonstrates that the cage is not merely an auxiliary electrode, but a configurable source of material. The ability to perform in-situ reduction of metal oxides using hydrogen plasma⁸ challenges the traditional dependence on expensive pure metal targets required in magnetron sputtering, offering a cost-effective route for depositing complex carbides and nitrides.

However, challenges remain. The optimization of cage geometry for large-scale industrial reactors requires further multiphysics modeling to ensure plasma homogeneity. Future research must focus on: (1) exploring the non-equilibrium plasma chemistry of oxide-reduction processes to tailor stoichiometry; (2) bridging the gap between laboratory-scale uniformity and industrial batch processing; and (3) expanding the “biomedical interface” of the technique, particularly for functionalizing heat-sensitive polymers using the remote plasma configuration.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR CONTRIBUTIONS

Conceptualization: Monção RM, Costa THC, and Sousa RRM; **Methodology:** Monção RM and Lima GG; **Research:** Monção RM and Lima GG; **Writing - First draft:** Monção RM and Lima GG; **Writing - Proofreading & Editing:** Costa THC and Sousa RRM; **Resources:** Sousa RRM; **Supervision:** Sousa RRM; **Final approval:** Sousa RRM.

DECLARATION OF USE OF INTELLIGENCE ARTIFICIAL TOOLS

The authors used AI-based editing tools during the preparation of this manuscript to improve readability and correct grammatical errors. The generated text was reviewed and validated by the authors to ensure the original scientific intent. No new data or scientific concepts were introduced by these tools.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

Coordenação de Aperfeiçoamento de Pessoal de Nível Superior 
Finance Code 001

ACKNOWLEDGEMENTS

Not applicable.

REFERENCES

1. Alves C, Araújo FO, Ribeiro KJB, Costa JAP, Sousa RRM, Sousa RS. Use of cathodic cage in plasma nitriding. Surf Coat Technol. 2006;201(6):2450-2454. <https://doi.org/10.1016/j.surfcoat.2006.04.014>
2. Sousa RRM, Araújo FO, Ribeiro KJB, Mendes MWD, Costa JAP, Alves C. Cathodic cage nitriding of samples with different dimensions. Mater Sci Eng.: A. 2007;465(1-2):223-227. <https://doi.org/10.1016/j.msea.2007.03.007>

3. Sousa RRM, Araújo FO, Gontijo LC, Costa JAP, Alves C. Cathodic cage plasma nitriding (CCPN) of austenitic stainless steel (AISI 316): influence of the different ratios of the (N 2/H 2) on the nitrided layers properties. *Vacuum*. 2012;86(12):2048-2053. <https://doi.org/10.1016/j.vacuum.2012.05.008>
4. Ribeiro KJB, Sousa RRM, Araújo FO, Brito RA, Barbosa JCP, Alves C. Industrial application of AISI 4340 steels treated in cathodic cage plasma nitriding technique. *Mater Sci Eng.: A*. 2008;479(1-2):142-147. <https://doi.org/10.1016/j.msea.2007.06.033>
5. Sousa RRM, Sato PS, Viana BC, Alves C, Nishimoto A, Nascente PAP. Cathodic cage plasma deposition of TiN and TiO₂ thin films on silicon substrates. *J Vac Sci Technol. A: Vac Surf Films*. 2015;33(4). <https://doi.org/10.1116/1.4919770>
6. Abreu LHP, Naeem M, Monção RM, Costa THC, Díaz-Guillén JC, Iqbal J, et al. The effect of cathodic cage plasma TiN deposition on surface properties of conventional plasma nitrided AISI-M2 steel. *Metals (Basel)*. 2022;12(6). <https://doi.org/10.3390/met12060961>
7. Lima LLF, Libório MS, Neto JFM, Coan KS, Rossino LS, Sousa RRM, et al. Plasma deposition of solid lubricant coating using AISI1020 steel cathode cylinders technique. *Mater Res*. 2023;26. <https://doi.org/10.1590/1980-5373-MR-2022-0623>
8. Medeiros Neto JF, Lima LLF, Vieira PS, Costa BT, Libório MS, Queiroz JCA, et al. Plasma deposition from cathodic cylinders: a technology for reduction of metallic oxides and deposition of wear-resistant films. *Surf Coat Technol*. 2024;488. <https://doi.org/10.1016/j.surfcoat.2024.131027>
9. Monção RM, Júnior EAA, Bandeira RM, Abreu Lima CD, Luz Lima C, Feitor MC, et al. Evaluation of corrosion resistance of thin films formed on AISI 316L Steel by plasma using hastelloy as cathodic cage. *Phys Status Solidi (A) Appl Mater Sci*. 2021;218(10). <https://doi.org/10.1002/pssa.202000578>
10. Sousa RRM, Costa THC, Costa JAP, Santos FEP, Nascimento IO, Souza IA, et al. Cathodic cage plasma deposition of DLC film on D2 steel substrate. 2019. Available from: <https://www.rroij.com/open-access/cathodic-cage-plasma-deposition-of-dlc-film-on-d2-steelsubstrate.php?aid=87535>
11. Naeem M, Fortaleza VC, Serra PLC, Lima CL, Costa THC, Sousa RRM, et al. Synthesis of molybdenum oxide on AISI-316 steel using cathodic cage plasma deposition at cathodic and floating potential. *Surf Coat Technol*. 2021;406. <https://doi.org/10.1016/j.surfcoat.2020.126650>
12. Silva LP, Naeem M, Díaz-Guillén JC, Brito MCS, Monção RM, Silva LGL, et al. Enhanced surface properties of 1080 eutectoid steel by cathodic cage plasma TiN deposition. *JOM*. 2025;77(2):539-548. <https://doi.org/10.1007/s11837-024-06949-w>
13. Silva LP, Libório MS, Sousa EM, Silva LGL, Monção RM, Brito MCS, et al. Enhancing wear resistance of AISI 1045 steel through duplex plasma treatment with vanadium cage. *JOM*. 2025;77(2):631-639. <https://doi.org/10.1007/s11837-024-07020-4>
14. Naeem M, Torres AVR, Serra PLC, Monção RM, Junior CAA, Rossino LS, et al. Combined plasma treatment of AISI-1045 steel by hastelloy deposition and plasma nitriding. *J Build Eng*. 2022;47. <https://doi.org/10.1016/j.jobe.2021.103882>
15. Naeem M, Shafiq M, Zaka-ul-Islam M, Bashir MI, Díaz-Guillén JC, Lopez-Badillo CM, et al. Novel duplex cathodic cage plasma nitriding of non-alloyed steel using aluminum and austenite steel cathodic cages. *J Alloys Compd*. 2017;721:307-311. <https://doi.org/10.1016/j.jallcom.2017.06.004>
16. Silva LGL, Brito MCS, Sousa EM, Nolêto BJS, Silva LP, Costa THC, et al. Effect of the vanadium layer on the wear resistance of the 1050 aluminum alloy coated by cathodic cage plasma deposition. *Stud Eng Exact Sci*. 2024;5(2):e7377. <https://doi.org/10.54021/seesv5n2-155>
17. Libório MS, Praxedes GB, Lima LLF, Nascimento IG, Sousa RRM, Naeem M, et al. Surface modification of M2 steel by combination of cathodic cage plasma deposition and magnetron sputtered MoS₂-TiN multilayer coatings. *Surf Coat Technol*. 2020;384. <https://doi.org/10.1016/j.surfcoat.2019.125327>

18. Sousa ME, Brito MC, Silva LP, Nolêto BJ, Silva LG, Monção RM, et al. deposition of metal oxides (Mo-Cu-Ti-Fe) using the cathodic cage deposition technique. *Int J Adv Eng Technol.* 2024;17:593-602. <https://doi.org/10.5281/zenodo.14731275>
19. Sampaio WRV, Brito MCS, Serra PLC, Monção RM, Sousa EM, Nolêto BJS, et al. Incorporation of TiO₂ nanoparticles in thin films deposited on AISI 304 stainless steel using the cathodic cage technique: a preliminary study. *Int J Adv Eng Technol.* 2024;17:528-541. <https://doi.org/10.5281/zenodo.14172994>
20. Santos RSM, Naeem M, Silva AL, Medeiros Aires M, Sousa RRM, Carvalho Costa TH, et al. Novel synthesis of zinc oxide on cotton fabric by cathodic cage plasma deposition for photocatalytic and antibacterial performance. *Int J Mol Sci.* 2024;25(18). <https://doi.org/10.3390/ijms251810192>